VOL. 36 JUNE 1960 NO. 6

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

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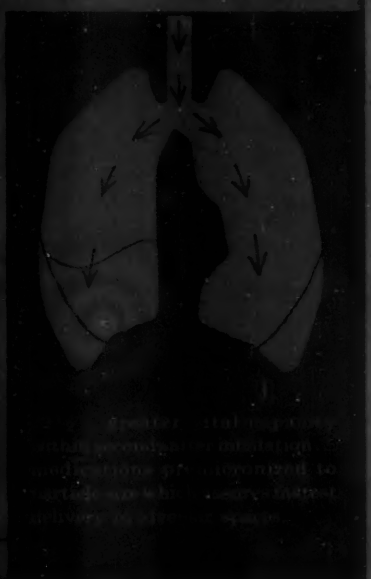

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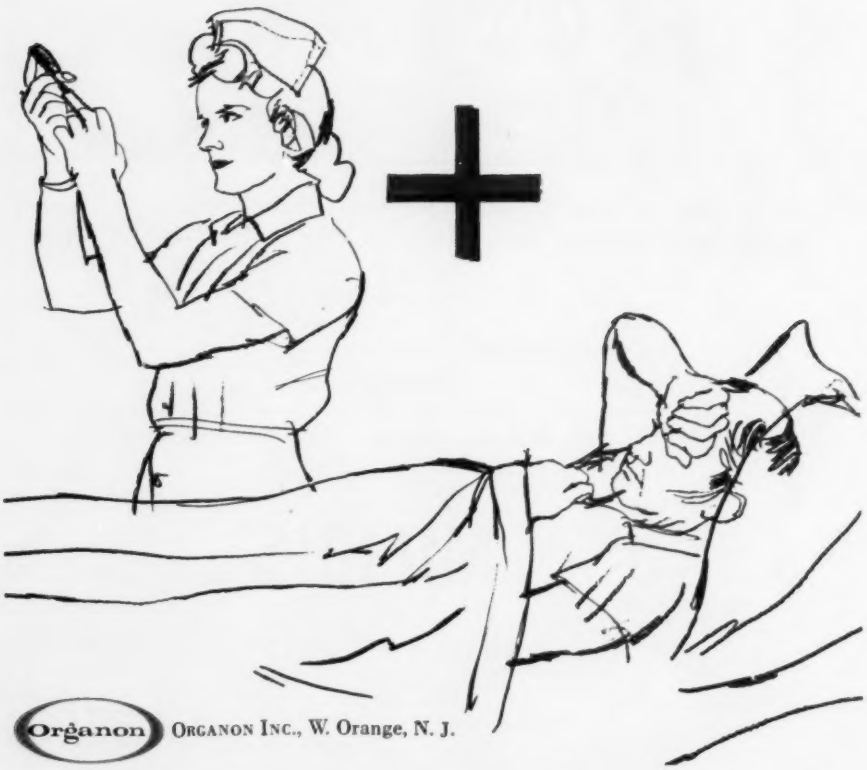

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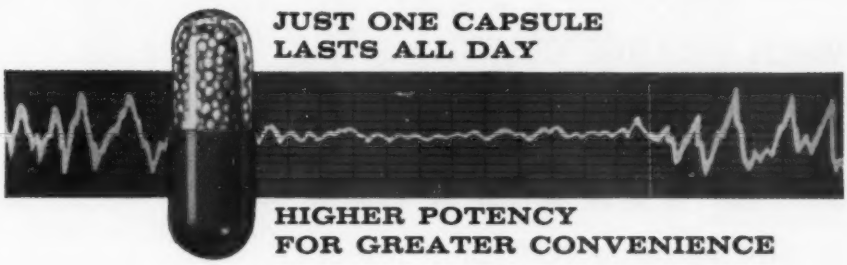

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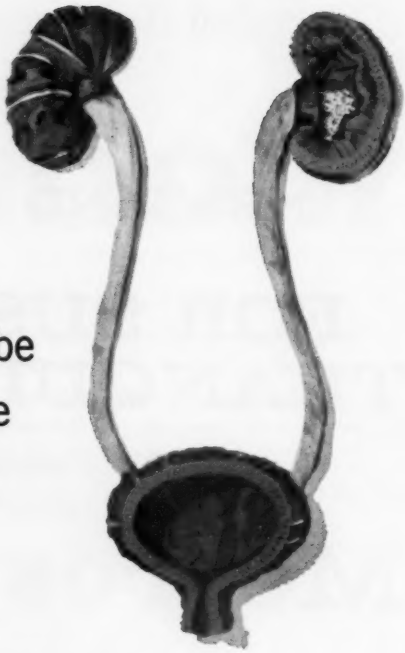

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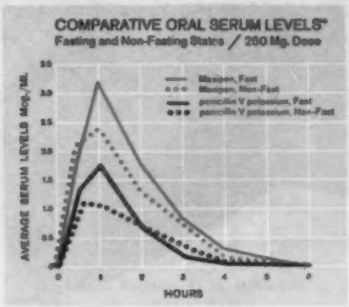

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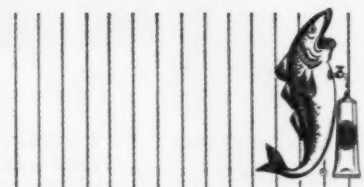

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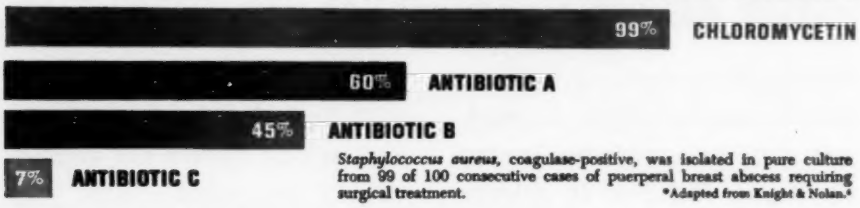

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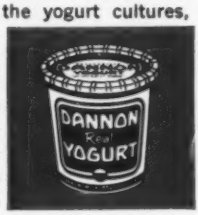

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

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BULLETIN OF
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VOL. 36, NO. 6 JUNE 1960

SOME CONTRIBUTIONS OF PNEUMOCOCCAL GENETICS TO THE ELUCIDATION OF BIOLOGICAL PHENOMENA*

ROBERT AUSTRIAN

Professor of Medicine, State University of New York College of Medicine
Downstate Medical Center, at New York City

One of the more interesting outgrowths of medical microbiology has been the utilization of pathogenic bacteria in studies designed to elucidate fundamental biological problems. Prior to the advent of chemotherapeutic and antibiotic agents, such organisms were the object of continuing scrutiny by many workers, and few among them were studied more intensively than was the pneumococcus. In his monograph published in 1936, White[1] included a bibliography of 1593 references related to this organism. Although little clinical interest in pneumococcus is manifested by physicians today, information accumulated previously from studies of pneumococcus has provided the basis for a continuing examination of its properties as a living cell. As a result thereof, infor-

* Presented at the Third Annual Postgraduate Week on *Research Contributions to Clinical Practice*, of The New York Academy of Medicine, October 6, 1959.

A portion of the work described herein was supported by research grant E-1018(C2) from the Institute of Allergy and Infectious Diseases, United States Public Health Service.

mation germane to several of the biological sciences is still being derived from investigations concerned with the genetics of this organism.

To begin, from the study of pneumococcus comes the most direct evidence concerning the chemical nature of genes, the determinants of inheritance. In 1928, the British bacteriologist, Griffith[2], reported his extraordinary findings relating to capsulation in pneumococcus. In studies designed to discover what conditions would favor alteration of avirulent noncapsulated pneumococci to the virulent capsulated state, Griffith employed several experimental techniques. Among them was the injection subcutaneously into mice of living noncapsulated organisms derived from capsular type II together with heat-killed capsulated type II cells. A number of the animals died and, from their blood, living virulent capsulated type II pneumococci were recovered. The experiment was repeated on another occasion, but with the substitution of heat-killed capsulated type I cells for the vaccine of pneumococcus type II employed initially. On this occasion, too, a number of the animals succumbed to pneumococcal infection, but the organism recovered at autopsy was not pneumococcus type II but type I! The result must have been a startling one, for a pneumococcus derived from a strain of one capsular type was found now to be producing the capsular polysaccharide of an organism of a different capsular type. The possibility that one or more viable type I pneumococci had survived in the "heat-killed" vaccine, accounting thereby for the anomalous results, concerned Griffith greatly and he repeated his experiments with scrupulous controls. The results were the same. His findings were confirmed by Neufeld and Levinthal[3]; and, shortly thereafter, a systematic study of the phenomenon was undertaken in the laboratory of Avery at the Rockefeller Institute, where investigations of the phenomenon of pneumococcal capsular type transformations were to continue over a period of nearly two decades. As a result thereof, Avery, MacLeod and McCarty[4] published in 1944 their important observation that the material extractable from capsulated pneumococcal cells which was capable of inducing the formation of a capsule by noncapsulated cells exposed to it was apparently deoxyribonucleic acid. For the first time, a specific biological activity could be ascribed to a chemical substance of this class. Another finding of note was that the deoxyribonucleate or "transforming principle" behaved within the cell as a self-replicating unit, for it could be recovered from the combined progeny

of the transformed cell in amounts far in excess of that required to induce the initial transformation. The attribution of genetic activity to deoxyribonucleate was consistent with observations on other than bacterial cells; for, in most cells, substances of this class are confined to the nucleus. Further studies of the chemistry of "transforming principle" by McCarty[5] and by Hotchkiss[6] have left little doubt that the conveyor of genetic information resides in deoxyribonucleate. Although it is known today that genetic information governing the structure of some viruses is contained in ribonucleate, no system permitting cellular or viral replication in the absence of deoxyribonucleate has yet been described.

The tentative structure of deoxyribonucleate proposed by Watson and Crick[7] appears suited in many ways for the incorporation and transmission of genetic data. They have propounded a model consisting of a two-stranded helix held together by the hydrogen bonds between complementary pairs of purine and pyrimidine bases. The sequence of bases is thought to determine the genetic information carried by the deoxyribonucleate molecule. If separation of the two strands of the helix can occur, two templates are provided thereby for the formation of new complementary strands of the same sequences as were present in those of the original molecule. Such a structure meets many of the requisites for genetic activity.

The demonstration of the chemical nature of the genetically active material in pneumococcus has provided, therefore, the first and most direct evidence of the biochemical nature of genes. If this inference is correct, then it should be possible to show that cellular characters other than the pneumococcal capsule are subject to hereditary control by deoxyribonucleates, and such has proved to be the case. The inheritance of a variety of cellular properties can now be modified in the transforming system in a fashion analogous to that demonstrable for capsular polysaccharide. Possession of a technique for controlling in a predictable fashion the inheritance of such cellular attributes has facilitated the collection of data pertinent to several biological disciplines, and it is with these data that the remainder of this report will be concerned.

By means of bacterial transformation reactions, it is possible to demonstrate the genetic basis of bacterial resistance to chemotherapeutic and antibiotic agents and to show that such resistance can be transferred

from resistant to sensitive cells by growing the latter in the presence of deoxyribonucleate of the former cells. In this fashion, resistance to sulfonamides, optochin, penicillin, erythromycin and streptomycin has been transferred from resistant to sensitive cells. Of additional interest is the fact that the mutational pathway to drug resistance may be reflected by the deoxyribonucleate of the resistant cell[8]. Resistance to high concentrations of streptomycin may arise in pneumococcus as the result of a single mutation or may be the result of multiple mutational steps. If cells of a streptomycin-sensitive strain of pneumococcus are exposed to the deoxyribonucleates of the one-step mutant, a high degree of resistance to this drug will be acquired by the cells transformed. A similar population of sensitive cells exposed to the deoxyribonucleates of the multistep mutant will acquire only a fraction of the resistance manifested by the donor of the genetic material, because the probability that a given cell will acquire more than one recognizable genetic factor in a single transformation is small. If re-exposed to the same preparation of deoxyribonucleates, however, additional increments of resistance may be acquired. In this way, the genetic history of the resistant strain is stored in its deoxyribonucleates. These observations provide direct confirmation of the genetic basis of drug resistance in bacteria. Their relevance to pharmacology and to clinical medicine is obvious.

It has been possible to show also by means of transformation reactions that the enzymatic activities of pneumococcus are subject to genetic control. The ability of cells to ferment salicin[9] and mannitol[10] can be modified by such reactions, as can certain of the enzymatic activities essential to the formation of the pneumococcal capsule[11]. Additional information of interest to biologists and to biochemists has been derived from a study of the adaptive enzyme, mannitol dehydrogenase, essential for the utilization by pneumococcus of the hexose alcohol, mannitol. An adaptive enzyme is one that is present in a cell in minimal quantities in the absence of its substrate, but which increases in amount after exposure to that substrate. The latter phenomenon is called induction. A cell which has been induced will utilize substrate immediately, whereas the uninduced cell will not do so until a finite time interval required for induction has elapsed. Marmur and Hotchkiss[10] have examined the deoxyribonucleates of uninduced and induced cells carrying the gene which determines the presence of the enzyme, man-

nitol dehydrogenase. When cells lacking this enzymatic activity are transformed with either of these deoxyribonucleates, they behave as uninduced cells; i.e., cells capable of forming the enzyme but failing to do so in the absence of exposure to the substrate. The experiment demonstrates that the deoxyribonucleate conveys only the ability to form the adaptive enzyme and that adaptation itself is a cellular function which is distinct from this genetic capability.

Transformation reactions have been useful in elucidating a variety of problems in the field of bacteriology. Although pneumococcus is known by the name *Diplococcus pneumoniae* in the United States, it is designated *Streptococcus pneumoniae* by British bacteriologists. Studies of several alpha hemolytic strains of streptococcus have shown them to be related genetically to pneumococcus. It has been possible to confer resistance to streptomycin upon a sensitive pneumococcus with the deoxyribonucleates of streptococci resistant to this drug and to carry out the genetic transfer of drug resistance in the opposite direction as well[12]. It is highly unlikely that these so-called "interspecific" transformations could be effected if there were not very close similarities in the deoxyribonucleates of the strains involved, and the results suggest an evolutionary relationship among the organisms concerned.

It is of interest that the efficiency of transfer of the genetic unit controlling resistance to streptomycin is usually lower in "interspecific" transformation than in "intraspecific" transformation. Interspecific transfer of the genetic determinants of more complex functions such as those controlling the formation of a bacterial capsule has not been accomplished to date.

The relation of bacterial colonial morphology to virulence has been a subject of interest both to bacteriologists and physicians. Although certain relationships appear to exist between these two attributes of bacteria, well-recognized discrepancies have disturbed what has appeared otherwise to be a useful correlation. Studies employing genetic recombination in pneumococcus have been helpful in clarifying this problem[13, 14]. It has been shown that the production of "rough" or "smooth" colonies is dependent primarily upon the mode of cellular separation after division, and that the presence or absence of the mucoid colonial state is dependent upon the amount of capsular polysaccharide produced by the cells comprising the colony. By the use of appropriate se-

lective cultural techniques and of genetic recombination in transformation reactions, it can be demonstrated in pneumococcus that mode of cellular separation after division and formation of a capsule are genetically distinct cellular properties. In addition, it can be shown in pneumococcus that virulence is dependent largely, if not entirely, upon the presence of the capsule and is independent of the mode of cellular separation after division. It has been found also that cells forming large amounts of capsular material give rise to mucoid colonies in which the pattern of cellular separation after division may be masked. The experiments show clearly the limitations of attempting to correlate colonial morphology with virulence and also the importance of examining bacterial cells rather than colonies in attempting to relate cellular properties to virulence.

Another finding arising from the genetic study of pneumococcus has been the recovery, following transformation, of strains which produce simultaneously two capsular polysaccharides[15]. These strains provide a new basis for serological cross-reactivity in this species and are therefore of immunological interest. Unlike strains which cross-react serologically by virtue of the fact that the molecules of their single dissimilar capsular polysaccharides contain common chemical subgroups, the strains with binary capsules produce two distinct capsular polysaccharides which are separable by a variety of techniques. That two distinct polysaccharides are produced can be demonstrated with precipitin reactions in an agar gel. These strains are of genetic as well as of immunologic interest, for they result from the simultaneous presence within the cell of the normal capsular genome of a strain which includes a uronic acid in its capsule together with the mutated capsular genome of a type III strain which has lost the ability to produce a capsule[11]. Loss of capsulation by the mutated type III strain results from loss of the ability to form glucuronic acid, an essential constituent of type III polysaccharide. When an appropriate heterologous capsular genome is introduced by transformation into the mutated type III cell without concomitant loss of the mutated type III capsular genome, the transformed cell is apparently able to divert some of the glucuronic acid formed under the influence of the newly introduced capsular genome to the production of type III polysaccharide; and both this capsular polysaccharide as well as that determined by the newly introduced capsular genome are expressed by the cell. The competition for glu-

curonic acid leads, however, to partial suppression of the polysaccharide determined by the newly introduced capsular genome as well as to augmented synthesis of type III capsular material. The phenomenon of binary capsulation provides, therefore, an example of genetic suppression and augmentation explicable in terms of a competitive biochemical reaction.

The epidemiological implications of genetic recombination are of considerable interest. It has been shown by Ephrussi-Taylor[16] that genetically distinct, noncapsulated variants of pneumococcus type III which are lacking in virulence may be recognized in transformation reactions, even though these organisms appear similar when examined by more conventional techniques. In such reactions, the deoxyribonucleate of one strain will interact with that in cells of the other strain in such a fashion as to lead to the restitution of the normal type III capsule. The relationship is a reciprocal one, either cell being capable of acting as the donor or the recipient of the deoxyribonucleate. In a reaction of this kind, the genetic units of two avirulent cell lines interact to give rise to a fully virulent pneumococcus. If recombinations of this kind were to occur under natural conditions, they might account for certain of the phenomena of epidemiology which evoked the doctrine of spontaneous generation in former times. In an experimental model such as the one described, two avirulent organisms interact to give rise to a virulent strain where none was present before. Such an event would provide circumstances which might account for the sudden appearance of a bacterium responsible for an explosive outbreak of infection. It is noteworthy that the capsule of meningococcus, an organism known for its epidemic potentialities, can also be altered hereditarily in transformation reactions[17].

Does bacterial transformation occur under natural conditions? Proof of such an event is lacking at the present time, though there exists circumstantial evidence compatible with an affirmative answer to this question. Pneumococcus produces a type-specific, somatic M protein which varies independently of type-specific capsular polysaccharide[18, 19]. Examination of numerous pneumococcal strains shows that different M proteins may be associated with organisms of the same capsular type, and that the same or closely similar M proteins may be found in pneumococci of different capsular types. One explanation for these antigenic relationships is that they may have arisen through genetic recombination,

for such recombinations can be accomplished in transformation reactions. Second, by employment of the technique of Griffith, it has been possible to demonstrate the occurrence of capsular transformation in a variety of mammalian species, including the rat, rabbit, guinea pig, cat and rhesus monkey[20]. In none of these species, however, has it been possible to demonstrate transformation of the pneumococcus in its usual habitat, the respiratory tract, be it normal or damaged by viral infection. It has been shown, *in vitro*, that transformation can be effected with deoxyribonucleate from a relatively small number of pneumococci[21]. Failure to demonstrate such genetic recombination in the respiratory tract may reflect ignorance of the conditions necessary for the occurrence of such a reaction rather than the inability of the reaction to take place. It should be pointed out also that spontaneous mutation in the direction of increased virulence may occur in pneumococcus and in other species of bacteria, and that it is not necessary to invoke genetic recombination as the sole means of accounting for the appearance of potentially epidemic strains of bacteria.

Since the discovery of the pneumococcal transformation reaction, other mechanisms of genetic recombination in bacteria have been recognized. A phenomenon akin to sexual recombination has been found to occur in the colon bacillus; and, in the salmonellas, part of the bacterial genome may be transported from one strain to another by bacterial virus known as bacteriophage. From the study of all these types of genetic recombination has come a wealth of material pertinent to a variety of biological problems. The essential similarity of living cells, the large numbers of bacterial cells which can be handled in the laboratory and their short generation time make bacteria suitable for the study of a wide diversity of biological phenomena. It may be anticipated that additional information of fundamental importance will be forthcoming from the continuation of such studies.

REFERENCES

1. White, B. *Biology of Pneumococcus*, New York, Commonwealth Fund, 1938.
2. Griffith, F. Significance of pneumococcal types, *J. Hyg. 27*:113-59, 1928.
3. Neufeld, F. and Levinthal, W. Beiträge zur Variabilität der Pneumokokken, *Z. ImmunForsch. 55*:324-40, 1928.
4. Avery, O. T., MacLeod, C. M. and McCarty, M. Studies on the chemical nature of the substance inducing transformation of pneumococcal types. I. Induction of transformation by a desoxyribonucleic acid fraction isolated from pneumococcus type III, *J. exp. Med. 79*:137-58, 1944.
5. McCarty, M. and Avery, O. T. Studies

on the chemical nature of the substance inducing transformation of pneumococcal types. II. Effect of desoxyribonuclease on the biological activity of the transforming substance, *J. exp. Med. 83*:89-96, 1946.

6. Hotchkiss, R. D. Études chimiques sur le facteur transformant du pneumocoque, *Colloq. int. Cent. nat. Rech. sci. 8*:57-65, 1949 (Unités Biologiques Douées de Continuité Génétique).
7. Watson, J. D. and Crick, F. H. C. Structure of DNA, *Cold Spr. Harb. Symp. quant. Biol. 18*:123-31, 1953.
8. Hotchkiss, R. D. Genetic chemistry of the pneumococcal transformations, *Harvey Lectures 49*:124-44, 1954.
9. Austrian, R. and Colowick, M. S. Modification of the fermentative activities of pneumococcus through transformation reactions, *Bull. Johns Hopk. Hosp. 92*: 375-84, 1953.
10. Marmur, J. and Hotchkiss, R. D. Mannitol metabolism, a transferable property of pneumococcus, *J. biol. Chem. 214*:383-96, 1955.
11. Austrian, R., Bernheimer, H. P., Smith, E. E. B. and Mills, G. T. Simultaneous production of two capsular polysaccharides by pneumococcus. II. Genetic and biochemical bases of binary capsulation, *J. exp. Med. 110*:585-602, 1959.
12. Bracco, R. M., Krauss, M. R., Roe, A. S. and MacLeod, C. M. Transformation reactions between pneumococcus and three strains of streptococci, *J. exp. Med. 106*:247-59, 1957.
13. Austrian, R. Morphologic variation in pneumococcus. I. An analysis of the bases for morphologic variation in pneumococcus and description of a hitherto undefined morphologic variant, *J. exp. Med. 98*:21-34, 1953.
14. Austrian, R. Morphologic variation in pneumococcus. II. Control of pneumococcal morphology through transformation reactions, *J. exp. Med. 98*:35-40, 1953.
15. Austrian, R. and Bernheimer, H. P. Simultaneous production of two capsular polysaccharides by pneumococcus. I. Properties of a pneumococcus manifesting binary capsulation, *J. exp. Med. 110*:571-84, 1959.
16. Ephrussi-Taylor, H. Transformations allogènes du pneumocoque, *Exp. Cell Res. 2*:589-607, 1951.
17. Alexander, H. E. and Redman, W. Transformation of type specificity of meningococci, *J. exp. Med. 97*:797-806, 1953.
18. Austrian, R. and MacLeod, C. M. Type-specific protein from pneumococcus, *J. exp. Med. 89*:439-50, 1949.
19. Austrian, R. and MacLeod, C. M. Acquisition of M protein by pneumococci through transformation reactions, *J. exp. Med. 89*:451-60, 1949.
20. Austrian, R. Observations on the transformation of pneumococcus *in vivo*, *Bull. Johns Hopk. Hosp. 91*:189-96, 1952.
21. Hotchkiss, R. D. Transfer of penicillin resistance in pneumococci by the desoxyribonucleate derived from resistant cultures, *Cold Spr. Harb. Symp. quant. Biol. 16*:457-61, 1951.

Symposium on*

PREVENTION OF OBESITY

Sponsored by the American Heart Association

Presiding: HERBERT POLLACK, M.D.

Chairman, Nutrition Committee, American Heart Association

Part II.

1. PROBLEMS RELATED TO THE CALORIC COST OF LIVING

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2. PROPHYLAXIS OF OBESITY IN THE ADULT

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3. SIMPLIFIED DIET PLANNING FOR THE PATIENT

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4. SUMMARY OF REPORTS

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* Held at The New York Academy of Medicine, May 26, 1959.

PROBLEMS RELATED TO THE CALORIC COST OF LIVING*

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Introduction

The formation and breakdown of various metabolites and the associated energy transfers within the body are intimately reflected by the total oxidative process and can be adequately assessed on a total body basis by careful measurements of oxygen consumption. If body composition is unchanged on a given dietary regimen, it therefore follows that one can also assess the daily energy demands of the body by measuring daily energy intake. In the past, most assessments of daily energy needs were made on the basis of the energy content of ingested food, with the exception of the considerable number of calorimetric measurements which took place in the late 1800's and the early 1900's. Although dietary surveys and other intake techniques are useful procedures, assessment of caloric requirements from food intake assumes that intake = output. In many areas of the world, intake and output are not equal and problems such as emaciation result in calorically "under-privileged" countries and obesity in "privileged" countries.

Newer information has increased awareness that energy intake and expenditure are mutually complementary in the construction of scales of caloric need. In addition, intake and expenditure data have been supplemented by nitrogen and electrolyte balance and body composition studies. In this way caloric needs can be appraised more physiologically and precisely than has been possible from energy intake information alone. Recently a surge of activity has occurred in the field of indirect calorimetric measurement largely because lightweight portable instrumentation has been developed which enables the investigator to get "on the job" to measure the energy expenditure of the worker without marked alteration of the task by the measuring equip-

* Presented as part of a Symposium on *Prevention of Obesity*, sponsored by the American Heart Association and held at The New York Academy of Medicine, May 26, 1959.

Reproduced through the courtesy of Buskirk, E. R. and Bass, D. E. *Science and Medicine of Exercise and Sports*, Harper & Bros. (To be published.)[4]

Fig. 1

The blackened area signifies the diurnal range in rectal temperature that may occur in a physically active individual.

ment. This boon should continue with the advent and utilization of new miniature equipment which will facilitate telemetering of information from the job site directly to the laboratory.

Several reviews have been prepared which provide detailed information about the caloric cost of various physical activities[1-3]. While these reviews provide considerable guidance, they do not provide complete information about the daily caloric requirements for a particular occupation. Since jobs change and recreational habits change and, indeed, man himself changes (man today is taller and heavier than his counterpart of 20 years ago), data on caloric requirements are usually somewhat dated. Thus, a continuing review of caloric needs is required.

In this presentation, an attempt at bringing our information "up-to-date" will not be undertaken, but rather, attention will be focused on some of the special problems related to the caloric cost of living, such as: 1) How do we spend our time? 2) What factors are important in altering the diurnal pattern of energy expenditure? 3) What are some of the newer methods of measuring energy expenditure? 4) Are caloric balance studies not feasible unless one has a calorimeter? 5) What attempts have been made to classify physical work and how can

TABLE I—COMPARISON OF TIMES SPENT PER 24 HOURS (h) LYING, SITTING AND STANDING BY PERSONS IN DIFFERENT OCCUPATIONS

Subjects and reference	*Time Spent*							
	Lying		*Sitting*		*Standing*		*Total*	
	h	min	h	min	h	min	h	min
Mine workers (Garry *et al.* 1955)	7	45	8	9	2	34	18	28
Clerks (Garry *et al.* 1955)	7	42	8	22	4	3	20	7
Cadets—first survey (Widdowson *et al.* 1954)	8	26	9	13	—	18½	17	57
Cadets—present survey	8	37	7	6	1	58	17	41
Schoolboys (Wiehl, 1944)	9	28	10	28	—	—	19	56
Factory workers* (Bransby, 1954)	8	34	5	11	—	21	14	6

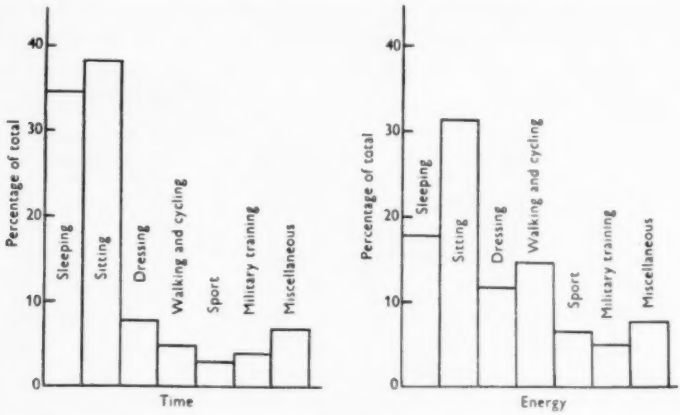
* Excluding working hours, which totaled 6 h 42 min/day.

Reproduced through the courtesy of Edholm, O. G. and Fletcher, J. G. *Brit. J. Nutr.* 9:286, 1955. (Cambridge University Press)[5]

these attempts be improved? Although partial answers to the above questions are attempted, treatment of each problem is fragmentary rather than comprehensive. Perhaps more questions are raised than answered, which further serves to emphasize our meager knowledge about the caloric cost of daily living in the modern age.

How do we spend our time? The factors that influence heat balance in man are shown in Figure 1[4]. If attention is confined to the heat production side of the scale, we find that metabolic heat production may be modified by muscular exercise, the "specific dynamic" effect of food, an increase in body temperature and shivering. Of these factors the importance of muscular exercise in increasing the daily heat production or metabolic rate is usually emphasized. When one exercises, energy expenditure can increase to 20 or more times the resting value; however, it is surmised that physical activities involving an increase above five-fold are rarely undertaken by the majority of men and women past the age of 25 or 30 years. But how active physically is the adult population at large? Fortunately, a few time-motion studies of certain occupations have been conducted, but little time-motion information is available, to the author's knowledge, for recreational activities.

As an example of industrial time-motion information, the summary table prepared by Edholm *et al.*[5] of times spent by various persons lying, sitting, and standing in various occupations is presented as Table I. From 17-20 hours per day are spent in resting positions, if Bransby's



Reproduced through the courtesy of Widdowson, E. M. *et. al. Brit. J. Nutr. 8*:148, Cambridge University Press[6], 1954.

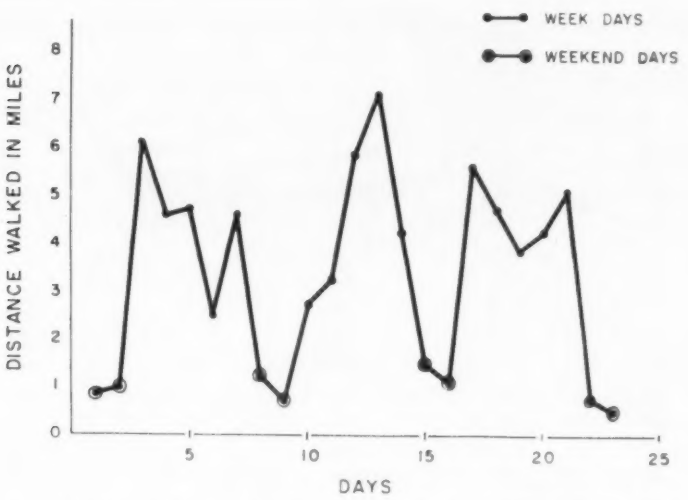
Fig. 2—Percentage of their time and energy which the cadets devoted to various occupations.

data for factory workers are omitted. (Presumably the factory workers spent part of the 6 hour 42 minute working period in a resting position, and the 14 hour total does not include this time.)

Although the major portion of the day may be spent in a resting position, how much of the daily caloric expenditure is associated with rest and how much with exercise? As an illustration, the data of Widdowson *et al.*[6] on British cadets are cited (Figure 2). Approximately 25 per cent of the cadets' time was spent participating in physical activity involving body movements, and approximately 45-50 per cent of the daily energy expenditure was associated with this activity. So far as young people are concerned, the British cadets studied by Widdowson are probably more active than the average student in the United States. An important point here is that little information of this kind is available in the U. S. literature; most of the above studies were British. An exception is the time-motion information obtained on soldiers from the United States and other nations while they participated in various military activities.* The data from soldiers, however, can only be applied in limited measure to the civilian population.

How constant is our energy expenditure from day to day? The daily energy expenditure for a given individual is not constant either

* Medical Nutrition Laboratory Reports, Fitzsimmons Army Hospital, Denver 8, Colorado.



Reproduced through the courtesy of Stunkard, A. J. *Psychosomatic Med. 20*:360, 1958.[7]

Fig. 3—(Patient A.A.) Variations in physical activity associated with the weekday-weekend cycle. On the ordinate are measured distances walked in miles, on the abscissa time in days. The circled points represent weekend days, the smaller points weekdays.

on a day to day or week to week basis. Probably the largest variation in weekly activity is produced by the weekend phenomenon.

Figure 3 was prepared by Stunkard[7] from pedometric data obtained from an obese subject who obviously "rested" each weekend and walked only a nominal number of miles (2.5 - 7.5 miles per day) during the work week. This active weekday, restful weekend activity pattern is one extreme; the other is provided by the individual who rushes home each Friday afternoon, dons his working or sporting clothes and proceeds to garden, rebuild the house or recreate all weekend. For this individual, energy expenditure may triple on weekends with respect to the work week. Most of us fall somewhere between these extremes. It would be an important contribution if daily, weekly and even seasonal frequency distributions could be established for the various energy expenditure patterns.

Several studies have been reported in which the daily energy expenditure by the obese individual has been less than that of his lean counterpart[8-10]. An example is provided by Table II, which shows a comparison of the daily and weekly walking distances traversed by

TABLE II—DISTANCES WALKED BY OBESE AND NONOBESE WOMEN*
(MILES)

Weekly Distances			*Daily Distances*	
Obese	*Nonobese*	*Difference*	*Obese*	*Nonobese*
10.0	28.5	—18.5		4.0 ± 1.0
23.0	17.5	+ 5.5	3.3 ± 0.8	2.5 ± 1.7
11.0	19.5	— 8.5	1.6 ± 0.7	
16.5	34.0	—17.5	2.4 ± 0.5	
8.0	22.8	—14.8		3.3 ± 1.8
7.8	16.5	— 8.7	1.2 ± 0.4	2.4 ± 0.3
12.0	39.5	—27.5		5.6 ± 2.4
10.7	23.0	—12.3	1.5 ± 0.5	
24.0	31.4	— 7.4		
8.3	30.5	—21.2	1.2 ± 0.4	4.4 ± 2.3
5.5	64.5	—59.5		
10.0	38.7	—28.7		
10.2	61.7	—51.5		8.8 ± 1.2
31.0	35.0	— 4.0		5.0 ± 1.5
Total				
14.4 ± 7.6	34.3 ± 14.5	—20.0 ± 16.2	1.8 ± 0.9	4.5 ± 2.5
		Significant at the 1% level.		

* The obese and nonobese women were matched for age and occupation. Distances walked were measured with pedometers.

Reproduced through the courtesy of Dorris, R. J. and Stunkard, A. J. *Amer. J. med. Sci. 233:622*, 1957.[8]

obese and non-obese women matched for age and occupation. On an average, the non-obese women walked more than twice as many miles per unit time as the obese. It should be emphasized that even the non-obese women did not walk extensively each day—two of the non-obese women averaged less than three miles per day[8].

How does our energy expenditure today compare to what it might have been 20 or more years ago? Recent information gathered from a questionnaire survey of Michigan State graduates suggests that a distinct decrease in physical activity has taken place[11]. Figure 4 shows a comparison of the estimated hours per day of "vigorous" activity obtained at several age levels. There seems to have been a decrease in physical activity through the years at all age levels. It is realized that this observation may be colored by nostalgic heightening of the degree of vigor with which activities were pursued earlier in life and recalled later.

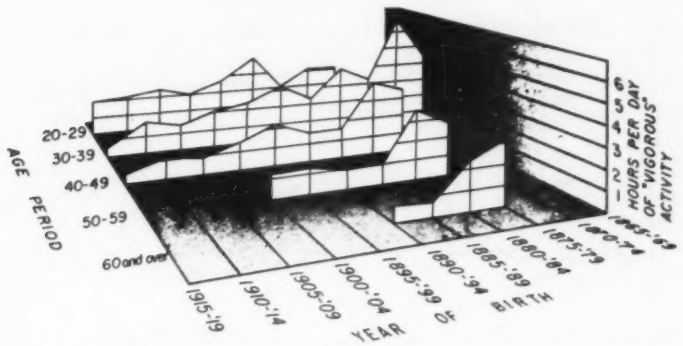


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Fig. 4—Comparison of subjects born in different years regarding hours per day of vigorous activity during various periods of life.

Diurnal variation in energy expenditure: No matter what the occupation of an individual, there are usually days when only a minimum of physical activity is undertaken. On these days the sequence of events may go something like this: sleep, arise, wash, shave, etc., breakfast, read, lunch, watch television, dine, watch television and retire. For people who are not bedridden, a similar schedule represents what might be called a "baseline" diurnal energy expenditure pattern. Of course many patterns exist depending on the habitual schedule for a given individual. Some of the factors which influence the diurnal pattern are discussed below.

(a) *Sleep:* In general, average energy expenditure for the night hours by many people approximately equals basal metabolic rate; it is oversimplification, however, to state this as categorical truth for all people, or for all nights for the same person. The energy expenditure associated with sleep is not constant; it varies hour by hour during the night and may vary considerably between nights in the same individual. This variation is associated with changes in the depth of sleep, body movements during sleep, the amount and kind of food eaten before retiring, and the environment in which sleep is attempted. Figure 5 shows the change in oxygen consumption during the night in four young adult males. Two of these subjects followed a consistent trend each night they were observed; however, two other subjects demonstrated oxygen consumption patterns that were quite variable from night to night[12].

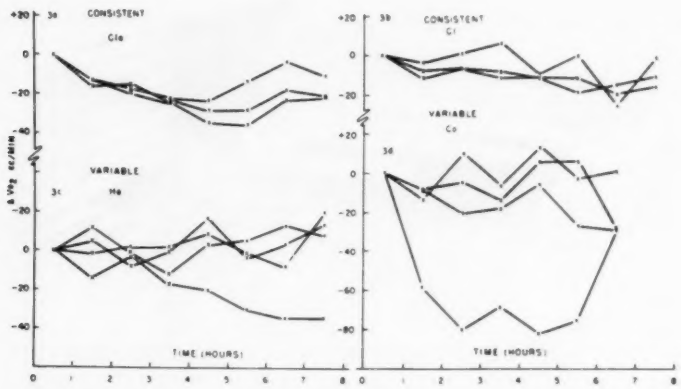

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Fig. 5—Intra-individual variation in pattern of O_2 consumption (Vo_2) throughout the night; *a* and *b* show examples of consistency while *c* and *d* show variability.

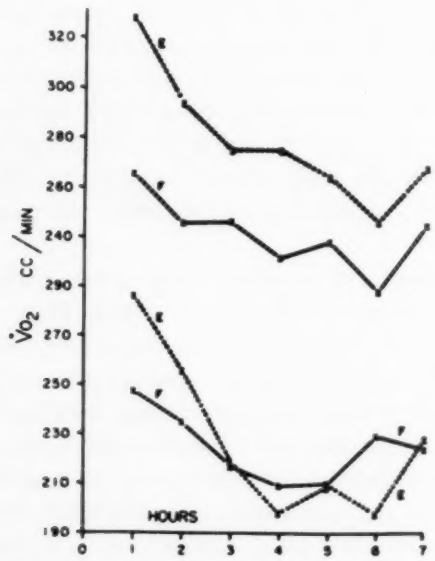

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Fig. 6—Oxygen consumption (Vo_2) of two men sleeping in arctic bags in —30 F air. Each curve represents six man nights.

E—Oxygen consumption after eating; meal fed immediately before retiring.

F—Fasting: last meal fed 5-6 hours before retiring.

TABLE III—HEAT PRODUCED DURING SLEEP (1 A.M. TO 7 A.M.) FOLLOWING DIFFERENT CONDITIONS OF ACTIVITY, AS REPORTED BY BENEDICT AND CARPENTER* (AVERAGE PER HOUR)

Subject	*Sleep after rest* cals.	*Sleep after moderate work* cals.	*Sleep after severe work* cals.	*Sleep after very severe work* cals.
E.O.	69.3	74.8	—	—
J.F.S.	60.4	65.3	—	—
J.C.W.	77.2	—	83.1	—
B.F.D.	69.8	—	83.3	—
A.L.L.	78.3	—	83.7	97.9

* All work ceased at least 7 hours before metabolism measurements began except in the case of very severe work in which work ceased but 1 hour before.

Original data recorded in: Benedict, F. G. and Carpenter, T. M., Carnegie Institution of Washington, Publication No. 126, 1910.
Reproduced through the courtesy of Edwards, H. T. *et al. New Engl. J. Med.*, Sept. 12, 1935.[15]

Although divergent patterns of energy expenditure during the night may also be shown by individuals regarded as consistent sleepers, others have also found that a rough classification of sleeping patterns is possible. Kleitman[13], for example, has found it convenient to divide adults into three groups according to the manner in which they rest:

1. absolute rest throughout the night
2. three hours of absolute rest followed by periods of relative and absolute rest
3. many periods of relative rest

If a continuous record of oxygen consumption is obtained for the night hours, one finds that physical activity can readily be discerned by an elevation in oxygen consumption.

Eating immediately before retiring may increase metabolic rate during the first few hours after retiring and may in certain individuals be associated with a higher than normal metabolic rate during the night[14]. This is shown in Figure 6.

If strenuous physical activity is undertaken during the day, energy expenditure during night hours may be elevated considerably. Table III shows results obtained by Benedict and Carpenter as reported by Edwards *et al.*[15] on several subjects after they had been subjected to work loads varying in severity. There seems to be a direct relationship be-

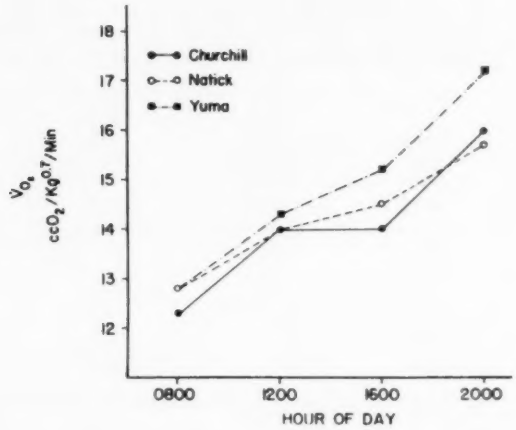

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Fig. 7—Change in resting oxygen consumption ($\dot{V}o_2$) throughout the day in three different climates which were respectively: Churchill, cold, winter; Natick, temperate, fall; Yuma, hot, dry, summer.

tween the severity of work performed during the day and the energy expenditure during sleep, even when the metabolic rate was measured several hours after work had ceased and the individual had retired.

(b) *Food:* In a recent series of experiments conducted on young adult male personnel in military service, it was concluded that the major factor affecting *resting* energy expenditure during the day was the "specific dynamic action" (SDA) of food[16]. Food exerted a greater effect on *resting* metabolism than either moderate physical exercise or the natural environment. Figure 7 shows the elevation in resting oxygen consumption that routinely occurred when three meals per day were eaten. The values plotted are mean values for eight men and were recorded after 30 minutes' rest just prior to eating the regular meal. No effect of natural climate could be observed (no difference between curves), although the men were outdoors continuously between meals and measurements in each climate. Only the later stages of the typical SDA curve after each meal are represented by each point plotted in Figure 7, which may be somewhat misleading unless a continuous curve of $\dot{V}o_2$ during the daytime hours is presented as a reference. This reference is provided by Figure 8, which shows oxygen consumption values obtained at 20-minute intervals throughout the day in one individual[16].

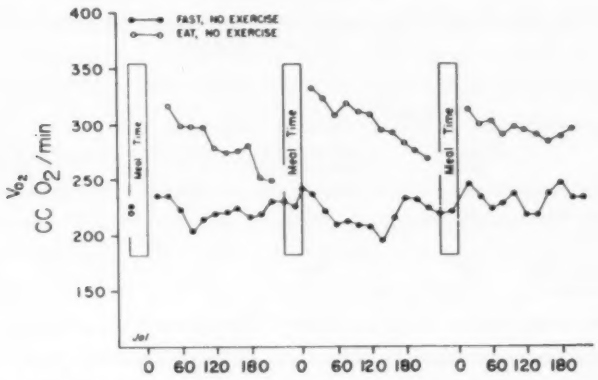

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Fig. 8—Variation in resting oxygen consumption (Vo_2) throughout the day when food was varied. Abscissa—Time in min. after meal.

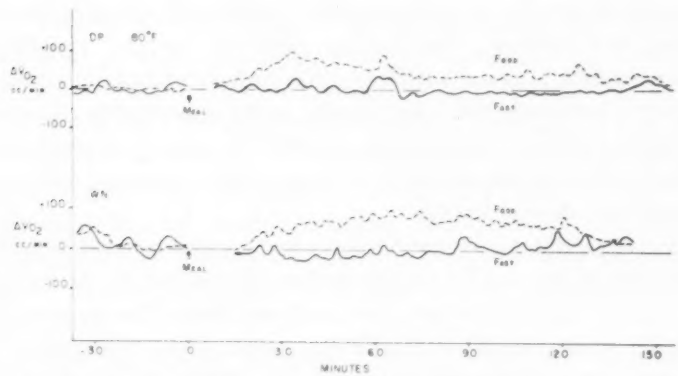


Fig. 9—Change in resting oxygen consumption (Vo_2) during fasting and after eating a 1000 Kcal liquid meal (40% of Kcal from protein).[17]

Peak oxygen consumption values in this subject were reached within 30 minutes after eating and declined steadily thereafter until the next meal was consumed. Note that a plot of the last measurement before each meal would reveal the same pattern as that shown in Figure 7.

With more sophisticated instrumentation a continuous record of oxygen consumption after eating has been obtained[17]. Pre- and postprandial values are shown for two subjects in Figure 9. Note that peak oxygen consumption values occur at different times in the two individuals and that muscular activity "spikes" are superimposed on rec-

TABLE IV—DAILY HEAT PRODUCTION OF PAIRS OF SUBJECTS ON EQUICALORIC DIETS

	Subjects R.B. & G.K.		*Subjects F.K. & G.S.*	
	Days on Diet	*Heat* Production (Kcal)*	*Days on Diet*	*Heat* Production (Kcal)*
Low-Protein Diet (38 gm/day)	52	4849	38	4680
High-Protein Diet (128.6 gm/day)	38	4830	52	4938
High minus Low		—19		258

* Values for heat production obtained by direct calorimetric measurements.

Reproduced by permission of the publisher from Table 1, Swift, R. W. *et al. J. Nutr.* 65:89, 1958.[38]

ords obtained both for the fasting and fed condition. It is apparently impossible to rest for several hours while awake and voluntarily suppress all muscular activity. Nevertheless, the SDA oxygen consumption pattern appears to stand out clearly for both individuals. In summary, the normal individual following regular meal habits exhibits a characteristic diurnal oxygen consumption pattern. The energy expenditure associated with physical activity is in large measure superimposed on this characteristic diurnal change.

One of the questions that has been investigated recently is whether a high protein diet fed for several weeks will continue to elicit a higher daily energy expenditure associated with SDA than a low protein diet[18]. Table IV shows the direct calorimetric results from two pairs of subjects who were alternately fed each diet. While the results are not unequivocal, it would appear that, at least in some subjects, adaptation to high protein diets may occur as shown by a reduction in 24-hour SDA. Presumably, the diurnal pattern would remain similar but the magnitude of the increase in energy expenditure after eating would be reduced in the "adapted" individual.

While the variations in total daily energy expenditure associated with sleep, a change in resting position and SDA are not large (5 - 15 per cent), it is interesting to consider the possible alterations in these modes of energy expenditure with gain or loss of obesity tissue. If excess caloric intake becomes habitual and excess obesity tissue is gained, there is the possibility that not only do rest periods become more frequent

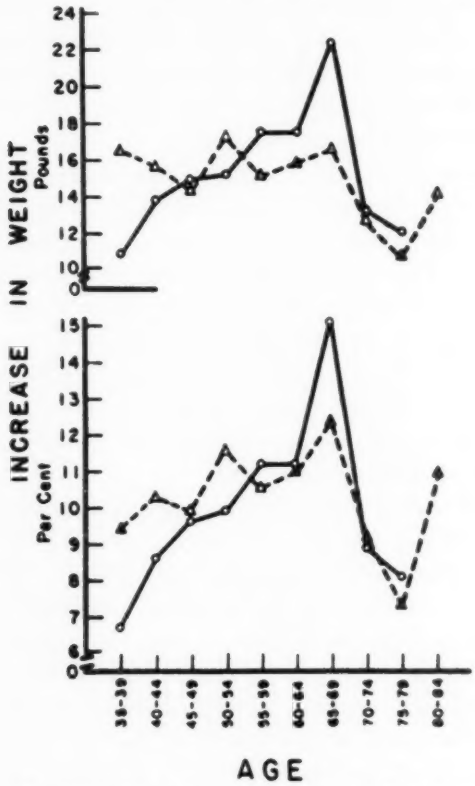
but that rest is more complete both when awake and asleep. As excess weight is lost, energy expenditure may well increase both because of more frequent change in body position and increase in spontaneous body movement. This possibility is under study in our laboratory (the "Metabolic Chamber") at the present time.

The SDA process tends to ameliorate the consequences of excess caloric intake. The greater the number of calories consumed, the larger SDA; however, the efficiency of the SDA mechanism in combating excess caloric intake is so low (seldom more than 20 per cent of the ingested calories associated with excess oxygen consumption and perhaps no more than 5 per cent of the excess calories consumed) that a gain in weight inevitably results from excess caloric intake. On the other hand, SDA is diminished on a sub-maintenance diet. Thus, SDA contributes little, if at all, to acceleration of weight loss when the obese person restricts his caloric intake.

(c) *Personal activities:* Almost everyone spends a portion of the day attending to personal necessities. Energy expenditure levels may be fairly high for these activities, depending on: the body position used, the speed at which the activities are performed and the length of time taken to accomplish each. Passmore and Durnin[2] prepared a summary table from information in the literature and list caloric expenditure values of from 2.3 - 4.0 Kcal/min. for washing, dressing, shaving, etc. On the average, perhaps one to one and one-half hours per day are spent on personal necessities, although a large inter-individual variation and a sex difference no doubt exist.

(d) *Walking and the transport of body weight:* Almost everyone walks for a portion of each day unless bedridden or otherwise incapacitated. There are many important factors which must be considered in an evaluation of energy expenditure for walking, such as: speed, weight transported, clothing worn, surface and incline, etc. It would require a long and detailed treatise to discuss adequately all of these factors; however, body weight, at least, deserves attention in this discussion.

Figure 10, taken from the study of Montoye *et al.*[11] on Michigan State graduates, indicates that on the average males gain weight after leaving college and that this trend continues into the sixth decade before it reverses. Because men become less active after leaving college, this increase in weight is largely obesity tissue, and transport of this excess weight during walking requires energy.

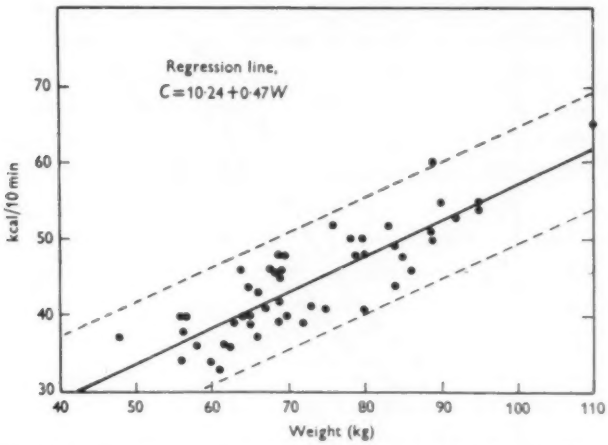


Reproduced through the courtesy of Montoye, H. J. *et al.*[31] *Longevity and morbidity of college athletes*, Phi Epsilon Kappa Fraternity, Indianapolis, Ind.

Fig. 10—Comparison of weight increase since leaving college of athletes and non-athletes. These values are derived by subtracting weight in college from present weight. Analysis of covariance indicated no significant difference in either weight gain in pounds or per cent gain ("between" variance smaller than "within" variance).

Mahadeva *et al.*[19] have investigated the relationship between walking energy expenditure and body weight. Their findings are presented in Figure 11. Both men and women were included in the series. An energy expenditure difference attributable to sex was not found. The coefficient for the slope of the regression line for Kcal/10 minutes on body weight was 0.47.

Rough calculations from the data of Mahadeva *et al.* and the load-carrying information assembled by Passmore and Durnin[2] from the work



Reproduced through the courtesy of Mahadeva, K. *et al. J. Physiol. 121:225,* 1953.[19]

Fig. 11—Energy expenditure during walking three miles/hr. The dotted lines show twice the standard error of estimate.

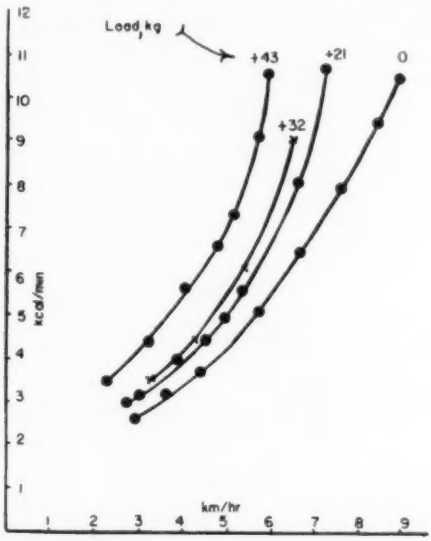
TABLE V—TABLE OF MEAN MINUTE-VOLUMES* FOR EACH WEIGHT

		Back				*Foot*			
Weight	0	4 kg	8 kg	12 kg	16 kg	0.6 kg	1.2 kg	1.8 kg	2.4 kg
Mean volume	25.06	26.02	26.38	28.91	31.21	24.78	25.73	25.45	26.59
S.E. of mean	0.49	←	0.46	→		←	0.46	→	

* Minute volume of ventilation.

Reproduced through the courtesy of Draper, J. *et al. J. appl. Physiol. 6*:301, 1953.[20]

of Brezina and Kolmer and Cathcart *et al.*, presented as Figure 12, indicate that the efficiency of transporting a load in a knapsack high on the back is about the same as transporting body weight of presumably "normal" composition. This same statement cannot be made, however, if the load is shifted to the hip or to an extremity. Table V shows that the increase in minute volume of ventilation (directly proportional to energy expenditure) is roughly two to three times as great if the load is tied to the foot as compared to the back[20]. Note in Figure 12 the rapid increase in energy expenditure with all loads if walking speed is increased. With addition of more and more weight, the slope of the energy expenditure curves increases. The obese person, then, is sub-



Reproduced through the courtesy of Passmore, R. and Durnin, J. V. G. A. *Physiol. Rev.* 35:801, 1955.[8]

Fig. 12—Energy expenditure carrying loads of different speeds. Data from Brezina and Kolmer and Cathcart et al.

jected to a severe energy expenditure penalty whenever he transports his excess weight, particularly if he hurries to catch a bus or otherwise proceeds at speeds above a "comfortable stroll" pace. In obesity, the load may or may not be distributed rather evenly throughout the body. If the obesity tissue is evenly distributed, transport of obesity tissue may be a very efficient method of load-carrying. On the other hand, if the extremities are unduly loaded, transport of obesity tissue may be a very inefficient process. If the addition of obesity tissue to the limbs becomes extensive, joint action may be inhibited and chafing may occur between the inner thighs. As a result, the process of moving the body becomes a major undertaking and is avoided whenever possible, because it is so inconvenient and uncomfortable to move.

Measuring "on the job" energy expenditure: "On the job" energy expenditure information has been facilitated by the improvement of old and the development of new instrumentation. Although the Douglas bag technique for measuring oxygen consumption has served admirably for a number of years (Douglas, 1911), new materials have made this method better than ever. Light-weight latex bags[21], light-weight cor-

rugated rubber tubing and light-weight rubber, plastic and aluminum respiratory masks and valves[1, 22] have reduced the load imposed on the subject during the measurement period. If the subject can carry light-weight equipment during the performance of his job, this eliminates the extra person sometimes used to carry the equipment for the subject. The extra person frequently interfered with the maneuverability of the subject, which led to grossly atypical results.

Another device, the Müller-Franz[23] modification of the Kofranyi-Michaelis combined gas meter and aliquoting system, which weighs about six pounds and can be easily transported by the working subject, has been widely used in Germany, Great Britain and to some extent in the United States.

More recently the IMP, or integrating motor pneumotochograph, was developed in Britain by H. S. Wolff[24]. This device measures expiratory flow rate and periodically withdraws a sample of expired air for analysis. The device weighs about four pounds, including the batteries to operate the required small motor and pump. A transmitter (an extra eight ounces) has been attached to the IMP, and ventilation volume information can be telemetered to the laboratory even though the subject is some distance away.

Energy balance studies: The results of representative energy balance studies, in which the above devices have been utilized, together with time-motion techniques for the measurement of energy expenditure, are presented in Table VI. A wide variety of working and living situations have been investigated in various places around the world. Note that most of the studies of energy balance are British, other than results obtained for military situations (Consolazio *et al.*[25], Welch *et al.* and Buskirk *et al.*[26]). On the average, the agreement between careful measurements of caloric intake and expenditure is good (± 10 per cent). It is interesting that, in most of the studies, caloric intake exceeds energy expenditure except in the one study involving dog sledging (Masterton *et al.*[29]). Whether this observation has any significance will depend on the results of similar studies in the future. The agreement obtained on a day to day basis[26] suggests that the daily difference between measured caloric intake and expenditure is random. With the addition of more energy balance studies to the series arbitrarily selected as "representative", it is suspected that an equal number of plus and minus differences will be found.

TABLE VI—REPRESENTATIVE DATA FROM THE LITERATURE FOR SIMULTANEOUS MEASUREMENTS OF DAILY ENERGY EXPENDITURE AND INTAKE

Reference	*No. of Subjects*	*Days Obs.*	*Activity*	*Intake*	*Expend.*	*Intake minus Expend.*
Consolazio *et al.*[25]	10	7	Military activities and recreation	3610	3471	139
Balke[27]	1	10	Mountaineering	5700	5150	550
Passmore *et al.*[28]	5	13	Male students, 5 days hard work 8 days sedentary	3610	3500	110
Widdowson *et al.*[6]	77	7	Military Cadets, normal training	3710	3420	290
Edholm *et al.*[5]	12	14	Military Cadets, normal training	3432	3416	16
Masterton *et al.*[29]	4	14	North Greenland Expedition, Base	3911	3581	330
also[30]	2 2	19 10	Dog Sledging	4770	5198	—428
Garry *et al.*[31]	10	7	Male clerks in colliery office	3040	2800	240
	19	7	Coal face workers	4030	3660	370
Welch *et al.*[26] Buskirk *et al.*[32]	8	17	Barrack & Bivouac Living in the Sub-arctic	3503	3280	223

Classification of physical effort: The diversity of tasks performed by man is enormous, yet we are faced with the problem of classifying physical effort in order to provide useful guidance to those responsible for health and welfare throughout the world. Many tasks are not easily classified because intricate, difficult to analyze movements are involved. In many cases, a human engineering study must be made of the man-machine-task interrelationships before further progress can be made. On the other hand, many tasks can be grouped according to the way the task affects common physiological variables, such as oxygen consumption and pulse rate.

Numerous arbitrary schemes have been devised for the classification of physical effort. For the most part, each scheme has only served the immediate needs of those responsible for it. A "classification" vocabulary acceptable to most potential users has not been adopted. To various in-

vestigators *hard* work may mean a level of work varying between 2 and 15 Kcal/min. Nor is it likely that an acceptable set of words and definitions will be adopted unless the lead of the respiratory physiologists is followed; they defined lung volumes and pulmonary function tests and standardized terminology. The classifications and definitions should be simple, convenient to use and acceptable to physiologists, nutritionists, clinicians and industrialists alike.

At least two recent attempts to grade physical work have appeared in the literature.

Christensen's classification[32] is based on the effort expended in various industrial jobs in the Swedish steel industry, which could easily be applied to professional, recreational and athletic activities as well. The physiological variables in Christensen's classification are metabolic rate and heart rate. Wells *et al.*[33], in an extension of the classification presented by Christensen, added criteria for the assessment of work level: ventilation rate and volume, R.Q., and blood lactic acid content. Wells *et al.* changed the terminology used by Christensen, dropped the 2.5 Kcal/min. level and added a 15 Kcal/min. level.

Because of the low levels of energy expenditure in many occupations, it is the author's feeling that an intermediate classification between 1.0 and 5.0 Kcal/min. is necessary. Ventilation volume should prove to be a useful addition to an adopted scheme, because of the possibility of telemetering ventilation volume as well as heart rate. There is a direct relationship between heart rate, ventilation volume and metabolic rate under a wide variety of conditions; therefore, these simple measurements should prove valuable in assessing "on the job" energy expenditure. It is felt that the measurement of blood lactic acid content would not add appreciably to a classification scheme because of the difficulties of drawing blood at the proper times for evaluation of the anerobic component for a given job.

On the basis of the ideas presented by Christensen and Wells *et al.*, review of the literature and first-hand experience, the combined scheme presented as Table VII may satisfy many requirements.

The physiological parameters related to metabolic rate that are easily measured, ventilation volume and heart rate, are included in Table VII. Since one purpose of such a table would be the estimation of the energy expenditure for a given task, it follows that the measurement of choice in this instance would be oxygen consumption. Measurement of oxygen

TABLE VII—CLASSIFICATION OF PHYSICAL EFFORT

Classification	$\dot{V}$	$\dot{V}o_2$	*M.R.*	*P.R.*
Very light	10	0.5	2.5	80
Light	10-20	0.5-1.0	2.5- 5.0	80-100
Moderate	20-35	1.0-1.5	5.0- 7.5	100-120
Heavy	35-50	1.5-2.0	7.5-10.0	120-140
Very heavy	50-65	2.0-2.5	10.0-12.5	140-160
Unduly heavy	60-85	2.5-3.0	12.5-15.0	160-180
Exhausting	85	3.0	15.0	180

$\dot{V}$ = ventilation volume in liters per minute

$\dot{V}o_2$ = oxygen consumption in liters per minute

M.R. = caloric expenditure in Kcal per minute

P.R. = pulse rate in beats per minute

The values listed apply to steady state work and also to peak effort as used in the diagram prepared by DuBois *et al.* (See Figure 13.)

consumption should take into account the oxygen debt, unless the work can be done in a "steady state" and measurements are made during the "steady state" period.

It should be emphasized that under certain conditions one or more of the variables listed in Table VII may fail to yield a valid estimate of the severity of the work but rather emphasize an emotional component such as fear, or fail to emphasize a "fitness" component, such as nutritional status during semistarvation. If pulse rate is the variable in question, fear or apprehension may yield abnormally high working pulse rates, whereas semistarvation produces abnormally low pulse rates.

The deficiency in Table VII is that body mass or size and physical fitness have not been taken into account. Perhaps the simplest method to correct for body size would be to express oxygen consumption and metabolic rate as the number of times basal metabolic rate, that is, two times, four times, etc. This type of expression has appeared in the temperature regulation literature and the term "met" for one times basal metabolic rate has been adopted. This approach assumes, however, that one either knows or is willing to estimate basal metabolic rate. For the time being it is felt that a correction for body size, while desirable, might only hinder wide adoption of a simple scheme for the classification of physical effort. Physical fitness for work is more difficult to cope with. In general, classification problems associated with age, disease, etc. could be

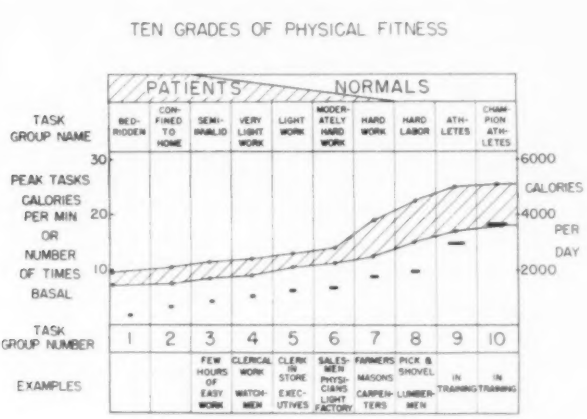


Fig. 13—*10 Grades of Physical Fitness*

At the top of the graph there is a box giving the usual division of experimental subjects into patients and normals. The line between these is made diagonal to show that there is a lapping of patients and normals when it comes to light work and even hard work, since some who are classified as patients can do hard work. The second box at the top of the chart shows 10 grades of activity ranging from bed-ridden patients to athletes, and at the bottom of the chart the various occupations are graded arbitrarily in the same manner. In the middle of the graph there are two curves representing roughly the estimated caloric expenditure for 24 hours for the people in the different groups. This estimate of caloric expenditure has been made from survey of the food consumption of people in different occupations, a method that is not very accurate but the best available at the present time. Below these two curves comes a series of bars representing roughly the peak tasks of the different occupations in terms of calories per minute or number of times basal. These could be represented in terms of oxygen consumption per minute but calories are used as they are better understood by most people. The height of the bar above the base line represents the calories of the peak tasks and the length of the bar is intended to represent roughly the duration of the task. Much more information is needed regarding the peak tasks in various American occupations as there are great differences in various institutions and individuals.

For groups 1 and 2, patients who are bedridden or confined to the home, the total caloric expenditure present per day is close to the hourly basal metabolism multiplied by 24 with perhaps an additional 6 per cent for the average specific dynamic action throughout the day. Allowance should be made for peak tasks and other forms of exercise and allowance for the higher basal metabolism found in fever and certain diseases. The peak tasks of patients in groups 1 and 2 are perhaps represented by the exertion involved in being admitted to the hospital or by the relatively hard work of using the bed pan or commode. Group 3, the semi-invalid, usually has as a peak task the work of getting into a chair or perhaps walking the length of the room. In these tasks, the oxygen consumption depends on the awkwardness of the individual and perhaps on the inefficiency of his muscles caused by disease. In recent times, a good many people classified as semi-invalids have been able to hold regular jobs and perform several hours of easy work.

(Illustration from an article submitted for publication by the late Eugene F. DuBois and co-workers, entitled "An Attempt to Classify Occupations in Ten Task Groups According to Physical Exertion, or According to the Amount of Physical Exertion Demanded.") To be published: *Proc. Amer. Phil. Soc. 104*, Feb. 1960. Reproduced by permission of the American Philosophical Society.

considered as those basically arising because of different levels of physical fitness. Perhaps the easiest way to express the values in a classification table is in relative terms, that is, relative to the maximal work capacity. Tests are available for assessing maximal working capacity[34-36]; however, one would have to either measure maximal working capacity or estimate it from submaximal values. Again, this may be an unnecessary complication and would thwart wide acceptance of a simple classification of physical effort.

Just before his untimely death, E. F. DuBois prepared a diagram (generously provided by his son, A. B. DuBois), in which he divided the adult population into task groups and presented data for both energy expenditure during peak effort and daily energy expenditure in one figure (Figure 13). The legend for the figure is largely self-explanatory. While one might quibble with the title, "10 grades of physical fitness", the choice of words for subgroups (Hard work vs. Hard labor), and his statement that physicians do *moderately hard work*, the energy expenditure summary is presented in a clear and useful fashion.

Work is usually intermittent and not continuous; therefore, time-motion information is also needed to tell us whether work should be called *hard* because of one peak effort, several peak efforts, or because of sustained effort below peak values. Thus, a rating or ratings of the work performed plus time-motion information plus summary information similar to that prepared by DuBois is essential for a more thorough physiological understanding of caloric requirements.

Summary

If a thorough physiological assessment of caloric requirements is undertaken, proper consideration should be given energy expenditure as well as caloric intake. Various factors influencing the diurnal, weekly and seasonal patterns of energy expenditure were discussed. These include sleep, the "specific dynamic action" of food and physical activity. The results of combining data on caloric intake and expenditure in order to establish assessments of energy balance for several "on the job" situations were mentioned together with a brief review of the newer techniques used to measure energy expenditure.

The problem of classification of physical effort was discussed in relation to: 1) definition and standardization of terms, 2) classification of the working and recreating population into subgroups according to

level of physical activity, and 3) the necessity for time-motion information.

Throughout the discussion the fact was emphasized that we, in the United States, do *not* have adequate information concerning the rate of energy expenditure associated with various occupations and recreational activities. There may be several reasons for this deficiency: 1) lack of a laboratory devoted to the study of industrial hygiene and work physiology*, 2) lack of interest on the part of investigators to undertake routine energy expenditure measurements on large numbers of people, and 3) lack, until recently, of miniaturized equipment for measuring energy expenditure without altering the task undertaken by the subject.

* Similar to the German Max Planck-Institut für Arbeitsphysiologie or the Finnish Institute of Occupational Health.

REFERENCES

1. Orr, J. B. and Leitch, I. Determination of calorie requirements of man, *Nutr. Abstr. Rev. 7*:509-29, 1938.
2. Passmore, R. and Durnin, J. V. G. A. Human energy expenditure, *Physiol. Rev. 35*:801-40, 1955.
3. Spitzer, H. and Hettinger, T. Tafeln für den Kalorienumsatz bei körperlicher Arbeit. Sonderheft der REFA-Nachrichten 1958. Hrsg. vom Verband für Arbeitsstudien REFA e. V., Berlin, Darmstadt Beuth-Vertrieb GmbH., 1958.
4. Buskirk, E. R. and Bass, D. E. *Climate and exercise.* To be published in *Science and medicine of exercise and sports*, Harper and Bros.
5. Edholm, O. G., Fletcher, J. G., Widdowson, E. M. and McCance, R. A. Energy expenditure and food intake of individual men, *Brit. J. Nutr. 9*:286-300, 1955.
6. Widdowson, E. M., Edholm, O. G. and McCance, R. A. Food intake and energy expenditure of cadets in training, *Brit. J. Nutr. 8*:147-55, 1954.
7. Stunkard, A. J. Physical activity, emotions, and human obesity, *Psychosom. Med. 20*:366-72, 1958.
8. Dorris, R. J. and Stunkard, A. J. Physical activity: performance and attitudes of a group of obese women, *Amer. J. med. Sci. 233*:622-28, 1957.
9. Johnson, M. L., Burke, B. S. and Mayer, J. Relative importance of inactivity and overeating in the energy balance of obese high school girls, *Amer. J. clin. Nutr. 4*:37-44, 1956.
10. Stefanik, P. A., Heald, F. P., Jr. and Mayer, J. Caloric intake in relation to energy output of obese and non-obese adolescent boys, *Amer. J. clin. Nutr. 7*:55-62, 1959.
11. Montoye, H. J. and others. *Longevity and morbidity of college athletes.* Phi Epsilon Kappa Fraternity, Indianapolis, 1957.
12. Kreider, M. B., Buskirk, E. R. and Bass, D. E. Oxygen consumption and body temperatures during the night, *J. appl. Physiol. 12*:361-66, 1958.
13. Kleitman, N. Sleep, *Physiol. Rev. 9*:624-65, 1929.
14. Kreider, M. B. and Buskirk, E. R. Supplemental feeding and thermal comfort during sleep in the cold, *J. appl. Physiol. 11*:339-43, 1957.
15. Edwards, H. T., Thorndike, A., Jr. and Dill, D. B. Energy requirements in strenuous muscular exercise, *New Engl. J. Med. 213*:532-35, 1935.

16. Buskirk, E. R., Iampietro, P. F. and Welch, B. E. Variations in resting metabolism with changes in food, exercise and climate, *Metabolism 6*:144-53, 1957.
17. Buskirk, E. R., Thompson, R. H., Moore, R. and Whedon, G. D. Equivalence of thermogenesis induced by food and by cold? *Fed. Proc. 18*:20, 1959.
18. Swift, R. W. and others. Effect of high versus low protein equicaloric diets on the heat production of human subjects, *J. Nutr. 65*:89-102, 1958.
19. Mahadeva, K., Passmore, R. and Woolf, B. Individual variations in the metabolic cost of standardized exercises; effects of food, age, sex and race, *J. Physiol. 121*:225-31, 1953.
20. Draper, J., Edwards, R. G. and Hardy, R. H. Method of estimating the respiratory cost of a task by use of minute-volume determinations, *J. appl. Physiol. 6*:297-303, 1953.
21. Ganslen, R. V. and van Huss, W. D. Ultralight (700 gram) apparatus for the study of energy cost of industrial work and sports, *Arbeitsphysiologie 15*: 207-10, 1953.
22. Hensel, H. Ein leichtes, am Kopf fixiertes Atemventil, *Arbeitsphysiologie 14*: 489-91, 1952.
23. Müller, E. A. und Franz, H. Energieverbrauchsmessungen bei beruflicher Arbeit mit einer verbesserten Respirations-Gasuhr, *Arbeitsphysiologie 14*: 499-504, 1952.
24. Wolff, H. S. Modern techniques for measuring energy expenditure, *Proc. Nutr. Soc. 15*:77-80, 1956.
25. Consolazio, C. F., Pollack, H., Crowley, L. V. and Goldstein, D. R. Studies on nutrition in the Far East. V. Caloric cost of work and energy balance studies, *Metabolism 5*:259-71, 1956.
26. Welch, B. E. and others, Buskirk, E. R. and others (Inter-laboratory report). *Caloric intake and energy expenditure in a subarctic environment.* U. S. Army Med. Nutr. Lab., Denver, Colo., 1957, Report No. 173; Quartermaster Res. Engineering Cent., Natick, Mass., 1957, EP33.
27. Balke, B. Energiebedarf im Hochgebirge, *Klin. Wschr. 23*:223-26, 1944.
28. Passmore, R., Thomson, J. G. and Warnock, G. M. Balance sheet of the estimation of energy intake and energy expenditure as measured by indirect calorimetry, using Kofranyi-Michaelis calorimeter, *Brit. J. Nutr. 6*:253-64, 1952.
29. Masterton, J. P., Lewis, H. E. and Widdowson, E. M. Nutrition and energy expenditure during a polar expedition, *Polar Rec. 9*:135, 1955.
30. Masterton, J. P., Lewis, H. E. and Widdowson, E. M. Food intakes, energy expenditures and faecal excretions of men on a polar expedition, *Brit. J. Nutr. 11*:346-58, 1957.
31. Garry, R. C., Passmore, R., Warnock, G. M. and Durnin, J. V. G. A. *Studies on expenditure of energy and consumption of food by miners and clerks, Fife, Scotland, 1952.* Med. Res. Council Spec. Rep. Ser. No. 289. London, HMS Stationery Off., 1955.
32. Christensen, E. H. Physiological valuation of work in Nykrappa Iron Works. In *Symposium on fatigue*, Ergonomics Res. Soc., W. F. Floyd and A. T. Welford, edits. London, H. K. Lewis & Co., Ltd., 1953.
33. Wells, J. G., Balke, B. and Van Fossan, D. D. Lactic acid accumulation during work; a suggested standardization of work classification, *J. appl. Physiol. 10*: 51-55, 1957.
34. Asmussen, E. and Hemmingsen, I. Determination of maximum working capacity at different ages in work with the legs or with the arms, *Scand. J. clin. Lab. Invest. 10*:67-71, 1957.
35. Astrand, P. O. and Ryhming. A nomogram for calculation of aerobic capacity (physical fitness) from pulse rate during submaximal work, J. appl. Physiol. 7:218-21, 1954.
36. Taylor, H. L., Buskirk, E. R. and Henschel, A. Maximal oxygen intake as an objective measure of cardiorespiratory performance, *J. appl. Physiol. 8*:73-80, 1955.

PROPHYLAXIS OF OBESITY IN THE ADULT*

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THE medical profession and the public in general have been told many times that obesity is the number one public health problem. No statistics are available today that can express the extent of the problem in accurate figures. One can make only fairly reliable estimates from the figures that are available. The reported results from several clinical centers devoted to the treatment of obesity present a pessimistic view with respect to the results achieved. A new approach to the problem is indicated. It is possible that a campaign for the prevention of obesity might be more effective than those devoted to the treatment of this condition.

The medico-actuarial height-weight tables of 1912 indicate definitely that the population as a whole gains weight with advancing years. For example, the average weight of a man 5 feet 10 inches tall, aged 25, is 71.3 kg. (157 lb.), but of a man aged 55 years, the weight is 78.6 kg. (173 lb.), a gain of 7.3 kg. (16 lb.). This evidence of actual gain in weight of the population may possibly give a clue to one of the causes of obesity.

What is universally accepted as the basic cause of obesity is an intake of calories in excess of metabolic demands. Obesity may result from an increased intake of calories in the presence of a constant output of energy, from a decreased output in the presence of a constant intake, or from any relative variation of the two. A great deal of attention has been given to the increased caloric intake aspect of weight gain. Undoubtedly this can be the principal cause of obesity, especially for those who become obese before early adulthood. Obesity most often develops in adult life when eating habits have been fairly well established. One may question the fact that a decrease in caloric expendi-

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ture is important in the weight gain of this group. A review and analysis of the "calorie cost of living" is indicated to determine the reasons for this suspected decreased caloric requirement.

The following five main factors determine the "calorie cost" of life: 1) age, 2) body size, 3) sex (these three comprising the basal metabolic requirements), 4) physical activity—work output, and 5) type of food—specific dynamic action. These factors are listed in the order of their relative importance for all persons except those who do extremely vigorous manual labor. (In the United States, mechanical horsepower has replaced, to a large extent, human caloric expenditure for very heavy physical work.)

Basal Metabolic Requirements

For the average white-collar worker and housewife, the basal caloric requirements constitute one-half to two-thirds the total calorie requirements for the day. This is expressed frequently in the textbooks. They state, "Calculate the basal requirements and add 50 per cent of this value to determine the total cost." If the basal requirements are such a large fraction of the total, it becomes necessary to analyze the basal caloric expenditure of adults.

The caloric requirement per unit of body weight starts to decrease shortly after birth. Up to about the age of 14 for females and 18 for males, the increase in body weight (growth factor) is greater than the metabolic decrement per unit of body weight. This results in an increasing total caloric requirement through adolescence that equilibrates in a person at about the age of 25 when optimum weight is achieved.

The decreasing metabolic requirements per unit of body weight become manifest in the presence of a constant intake. According to DuBois, for a man, aged 25, the basal caloric requirement is 37.4 calories for each square meter every hour, and for a man, aged 55, it is 35.3 calories per square meter per hour. A man 5 feet 10 inches tall, who weighs 71.3 kg. (157 lb.) has a surface area of 1.87 sq. m., and a man of the same height, who weighs 78.6 kg. (173 lb.) has a surface area of 1.91 sq. m.

Thus, the man weighing 71.3 kg. at age 25 requires 69.9 calories per hour, and the man weighing 78.6 kg. at age 55 requires 67.4 calories per hour. In 24 hours they require, respectively, 1,678 calories and 1,618 calories. But if the man at age 55 had retained his weight of 71.3 kg., he

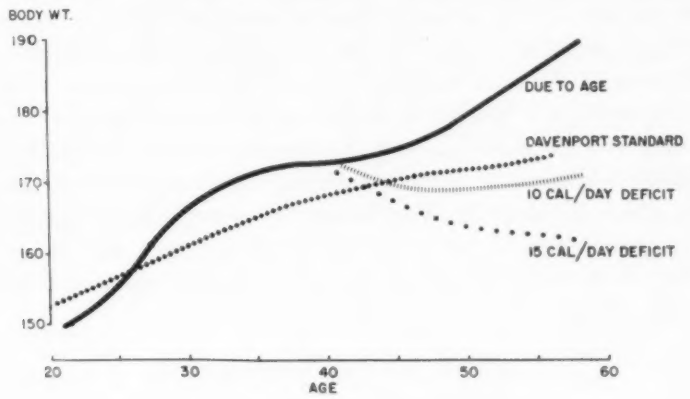

Figure 1

would require only 66.0 calories per hour or 1,584 calories in 24 hours.

Figure 1 shows a curve drawn from data obtained by the calculation of the small decrement in caloric requirements associated with the aging process for a hypothetical man, 5 feet 10 inches tall, who consumes food providing 2,800 calories a day over a period of years. The basal caloric requirements are corrected downward for aging and upward for each increment in weight gain. The net result is a positive caloric balance. The value of 3,500 calories is used as the equivalent of one pound in body weight for conversion purposes. The curve is essentially S-shaped with the plateau in the middle 40's age group. If one superimposes on this curve another one drawn from the age, height, and weight tables published by the Life Insurance Actuarials in 1912, it is obvious that the trend of the curve based upon averaged actual measurements of a large cross section of the population is almost identical to the hypothetical curve drawn from the assumptive data. The similarity in the curves allows one to present certain hypotheses with respect to the overweight person found in aging population groups.

Small increments of positive caloric balance over a period of time can result in pronounced obesity. This increment can be due to decreasing basal metabolic requirements. When this age decrement is coupled with decreasing physical activity, a common phenomenon in the present day population, a marked gain in weight can result. A difference of 10 to 15 calories per day, over a period of 15 years, can cause a difference of 4.5 to 6.8 kg. (10 to 15 lb.) of body weight. It will

be shown later in this discussion that the difference between sitting and standing is sufficient to alter caloric expenditure by this increment. By application of the same reasoning of small increment changes to actual physical work, it is possible to emphasize the importance of activity in a weight control program. Very little can be done to change the basal metabolic requirements without upsetting the homeostatic mechanism upon which life depends. This leaves two possibilities to prevent the slow accumulations of fat; a decrease in caloric intake, and an increase in the calorie requirements of the other factors, work and specific dynamic action.

Physical Activity Requirements

The energy expenditure of individuals may vary considerably. This is due to both a variation in the amount of work that they perform and in the individual variations in the calorie cost of such work. Certain components in the different work outputs of individuals are obvious and easily understood. A specific example illustrates this. Two men are working together to make a hole in a block of granite. One man stands still directing the cold chisel with a pair of tongs, while the other swings the heavy sledge hammer down onto the head of the chisel, picks it up and swings again. Swinging a sledge hammer is a type of work that is independent of body size. The foot-pound expenditure depends on the size of the hammer and the distance through which it is swung. A small man will spend approximately as much energy lifting a sledge hammer as does a large man.

The calorie cost of any type of activity that involves the whole body, such as walking, varies with the size of the body and, more specifically, with total body weight. In actual experiments, a man weighing 61 kg. (134 lb.) who walked for one hour at a rate of 3.5 mph. spent 261 calories. A man weighing 91 kg. (200 lb.) expended 366 calories walking the same distance at the same speed, and a man weighing 99 kg. (218 lb.) expended 409 calories. The addition of dead weight to the shoulder of an individual increases his caloric expenditure in the same order of magnitude. A man weighing 68.2 kg. (150 lb.) used 98.8 calories to walk one mile. Forty kilograms (88 lb.) of weight were then put on his shoulder, and the calorie cost of the mile increased to 142 calories. It is no wonder that small people complain that they gain weight so easily.

TABLE I—ENERGY EXPENDITURE IN WALKING AS AFFECTED BY VELOCITY AND WEIGHT

Speed, Mph.	*Weight, Kg. (lb.)* 54.5 (120)	63.6 (140)	72.8 (160)	81.8 (180)	91 (200)
2.0					
Calories/min.	2.6	2.9	3.2	3.5	3.8
Calories/hr.	156	174	192	210	228
Calories/mile	78	87	96	105	114
2.5					
Calories/min.	3.1	3.5	3.8	4.2	4.5
Calories/hr.	186	210	228	252	270
Calories/mile	74	84	91	101	108
3.0					
Calories/min.	3.6	4.0	4.4	4.8	5.3
Calories/hr.	216	240	264	288	318
Calories/mile	72	80	88	96	106
3.5					
Calories/min.	4.2	4.6	5.0	5.4	6.1
Calories/hr.	252	276	300	324	366
Calories/mile	72	79	86	93	105
4.0					
Calories/min.	4.7	5.2	5.8	6.4	7.0
Calories/hr.	282	312	348	384	420
Calories/mile	71	78	87	96	105

It is a common fallacy to consider the speed of walking as an important factor in the calorie cost and to attribute the slowing down of the speed by the elderly person as contributing to the weight gain. Table I is based on the work of Margaria. It demonstrates clearly that walking a mile, regardless of the rate of speed, costs essentially the same number of calories per unit of body weight. In fact, the cost in calories per mile is somewhat greater at the slower pace.

There are other seemingly insignificant differences in the daily habits of people that account for some weight gain differences over a long period of time. The differences in the calorie cost between lying down, sitting, standing quietly and standing while moving in a limited area, have been measured (Table II). These differences may not seem large, but when multiplied by the total minutes during the day, they loom larger. For example, there is a difference of almost 9 calories an hour between sitting quietly and standing quietly. Those people who

TABLE II—ENERGY EXPENDITURE IN VARIOUS ACTIVITIES

	Calories/Min.	*Calories/Hr.*	*Difference between each Preceding Activity, Calories/Hr.*
Sleeping	1.09	65.40	.....
Lying down	1.26	75.60	10.20
Sitting	1.35	81.00	5.40
Standing	1.50	90.00	9.00
Standing, light action	2.60	156.00	66.00

TABLE III—ENERGY EXPENDITURE IN TRAVELING A DISTANCE OF 2.5 MILES

	Speed, Mph.	*Time Consumed*	*Caloric Expenditure*
Walking	2.5	1 hr.	210
Cycling	5.5	27. min.	122
Driving	25.0	6 min.	17

never stand still may burn 66 calories an hour more than their relaxed brother. In 70 hours, the former burns the equivalent of 1 pound of body weight more than the other (calculate 3,500 calories per pound of body weight).

The mechanization of life in recent years has had an influence on the caloric expenditure. Some people have compensated by using this new leisure time for active sports, whereas others have not. For example, a man lives 2.5 miles from his work. Table III shows the caloric expenditure of walking, bicycling, or driving his automobile to work. If cycling and driving are compensated for by adding the caloric requirements of standing for the remainder of the hour, the results shown in Table IV are found.

A typist who is 63 in. tall and weighs 54.5 kg. (120 lb.) uses 87.7 calories per hour in using the standard mechanical typewriter. The same typist using an electrical typewriter expends only 72.9 calories per hour. For this individual there is a difference of 14.8 calories an

TABLE IV—ENERGY EXPENDITURE IN ONE HOUR WHEN TRAVELING A DISTANCE OF 2.5 MILES

	Time Consumed	*Standing Min.*	*Caloric Expenditure*
Walking	1 hr.	0	210
Cycling	27 min.	33	171
Driving	6 min.	54	97

hour, and for six hours of actual typing, there is a saving of 90 calories with the power typewriter. For a five-day week, it amounts to 450 calories; in 10 weeks this can be the equivalent of a pound of body weight, assuming a constant intake.

A farmer driving a tractor with a standard steering wheel during cultivation of a field expends 85 calories per square meter per hour, but if he uses power steering, he expends only 68 calories per square meter per hour. For a man who is 5 feet 10 inches tall, weighing 68.3 kg. (150 lb.), with a surface area of 1.85 sq.m., this means 157 calories versus 126 calories every hour; in an eight-hour day, this is an 8.6 per cent difference in total daily caloric requirement. This saving is small when compared to the caloric requirement of the farmer who walks behind his horse-drawn plough. He expends 400 calories per hour.

The difference in calorie expenditure between two men on a week-end can be considerable. One man plays 18 holes of golf, walking about four miles in three hours, and expends 950 calories. The other man gardens for three hours and expends only 580 calories. One man goes out in the evening and dances for an hour, and sits and talks for two hours, spending a total of 400 calories; the other man just sits for three hours and spends 275 calories.

Table V is presented to show the variations in caloric expenditures with various activities. It must be pointed out that in certain activities, such as walking, the motion is constant and the expenditure uniform throughout the time. In other activities such as tennis and football, the motion is intermittent. The values expressed are for the periods of motion only. For an hour of tennis, a player may be in motion only about one-third of the time; the rest of the hour must be calculated as standing only.

TABLE V—CALORIC COST OF DAILY LIVING ACTIVITIES AND SPORTS IN MEN

Normal Activity	*Cal./Min. Sq. M.**	*Sports*	*Cal./Min. Sq. M.**
Sitting, normal	0.70	Football	5.04
Sitting, reading	0.70	Basketball	4.31
Sitting, eating	0.80	Pingpong	2.42
Sitting, playing cards	0.83	Bowling	4.06
Resting in bed	0.58	Swimming	6.06
Standing, normal	0.81	Golfing	2.76
Standing, light activity	1.41	Tennis	3.50
Personal toilet	1.09	Squash	5.00
Shower	1.84	Badminton	1.91
Dressing	1.84	Rowing	4.00
Making bed	2.64	Sailing	1.30
Shining shoes	2.11	Snooker pool	1.50
Mopping floor	2.67	Dancing	2.00
Walking indoors	1.68	Riding	1.50
Walking outdoors	3.07	Boxing, sparring	5.00
Walking downstairs	3.80		
Walking upstairs	10.00		
Kneeling	0.68		
Squatting	1.12		
Washing clothes	1.46		

* Based on basal metabolic rate of 0.59 calories per minute per square meter of surface area.

The importance of the calorie expenditure factor in the development of moderate obesity in the adult should not be minimized. It is important for persons to recognize that certain physiological changes take place in the human body that demand readjustment of the work and play habits, or special attention to food intake. Small increments of excess intake and small decrements of increased output together can be responsible for much adult obesity.

The prevention of obesity is a somewhat different problem than the treatment of an existing obese state. The prevention of obesity recognizes that the caloric intake should be equal to the metabolic demands of the body. The body weight is the best indicator of this equilibrium. Ordinarily when we think of obesity, we think in terms of creating a calorie deficit, the extent of which will determine the rate at which the body weight is reduced. We have discussed here many of the aspects involved in the activity or in the total metabolic demands of the body.

It has been pointed out that there are energy equivalents for units of work and for units of food. Consequently food and work can be made to equilibrate in order to establish and maintain this level.

The statement is made frequently by the physician and the layman, "You have a weight problem, you must cut out bread and potatoes." The acceptance of this type of traditional thinking is one that leads to a great many problems. Whenever a food item is eliminated completely from the diet the possibilities of creating a nutritional imbalance become great. Bread, in our current day civilization, particularly the enriched breads, supplies almost 40 per cent of the B vitamin requirements. The elimination of this food from the diet may lead to disturbances in the B vitamin balances. Potatoes supply a fair amount of vitamin C. They supply an alkaline residue, or ash, to the body, which is important in the maintenance of the homeostatic mechanisms.

The general principle of prevention of obesity in the diet can be summed up very briefly. One must watch the scale weight of the body. When you observe a rapid change in body weight, in the order of one or two pounds a day, or even five pounds a week, one must suspect that this rapid change is due to changes in water balance rather than in changes in caloric equilibrium. Figure for yourself, a change in body weight of one pound involves a loss or gain of approximately 3500 calories. If you lose a pound in one day, that means that you have burnt up 3500 calories more than you have taken in. The average individual of medium height and normal weight lying in bed and doing nothing will not burn more than approximately 2200 to 2300 calories under these conditions. Even a complete fast for one day will not bring about a calorie deficit of 3500 calories.

It is conceivable that if an individual walked approximately 13 miles in the course of a day without eating food he could bring his caloric expenditure up to a level where a loss of one pound could be achieved. This, as you recognize, would not be a common occurrence. One should watch weight changes on the basis of a week or month, rather than on a day to day basis. The fluctuations in water balance will obscure changes in body weight on short-term measurements. When one observes a gain in weight over the course of a month, or a few months, it is time to review one's habits for this period of time. The review must include a consideration of a decrease in activity in one form or another, or whether there have been more cocktail parties, or whether the desserts have been

more tempting than in the past. When the weight increase is observed over the course of a year, maybe just a few pounds, as indicated in the chart earlier, then we know the individual has been maintaining a constant intake of food and the same type of activity level, but has failed to recognize the fact that his food requirements are decreasing. He must compensate by increasing his activities, or by decreasing his food intake. Ordinarily one thinks in terms of the elimination of the foods of high caloric densities. In reduction regimes in the past the attempt has been to achieve a very low fat intake. In recent years, the safety of the extremely low fat intakes, or the elimination of all the visible fat from the diet, has been questioned. The possibility of some type of metabolic change because of this failure to supply the body with some fats has been raised. Investigators like Kinsell, Ahrens and Page have shown that the intake of the poly-unsaturated fatty acids will maintain a lower blood cholesterol level over longer periods of time than simply reducing the fat content of the diet. If one is to follow the advice of these people, then it is important to include in one's daily diet some type of poly-unsaturated vegetable oil, in an effort to maintain a low serum cholesterol level. There is no proof that maintaining a low serum cholesterol level will avoid atherosclerosis. We do not have enough knowledge about it at the present time but the suspicion is there. The people who work in the field may disagree with each other, and at times with themselves, but the fact remains that many physicians today, just to play it safe, are advising their patients to include some of the vegetable oils in their diet daily, be it cottonseed or any other type. In weight maintenance, or prevention of obesity, this is of course very simple because the dietary allowances of most people will allow for the inclusion of some salad oil, or vegetable oil in cooking, in the diet without exceeding the caloric requirements for the day.

Miss Schur will present to you a concept, which I have discussed with her, of what we call a "module diet". The module, or the unit, of food is equated to the unit of activity, and food and menu are discussed with the patients in terms of these very simple units.

SIMPLIFIED DIET PLANNING FOR THE PATIENT*

SYLVIA SCHUR

WHEN you sit across the desk from a patient who needs help in diet planning—where do you begin?

His problem may be affected by the lower energy costs of modern life, or by a pathological or hereditary factor. It may have anthropological roots. Prophylaxis may be essential. Whatever the individual differences, all men and women who need help in diet planning have one thing in common: a four-letter word which spells man's most lasting pleasure, food.

Food, like people, can be divided into the fat and the lean, but most patients don't know one from the other. In our affluent era we make this division more complicated. An enormous variety of prepared and convenience foods brings not only more, but often higher-calorie, dishes to everyday meals. It is as easy to reheat frozen French-fries as to boil potatoes. Why serve steamed asparagus when asparagus Hollandaise is handy; or a broiled veal chop when you can have it smothered with sauce and cheese *parmigiano* style?

Americans are *nouveaux riches* in attitudes toward our new affluence in food. This attitude has helped build a dietary pattern in which at least 40 per cent of our calories come from fat.

The first challenge in diet training is to teach a patient to know high calorie foods. I have here what Designer Raymond Loewy has called the most perfect of package designs—an egg. Let's crack its shell, and separate it: white 17 calories, yolk 60 calories. That 60 calorie yolk has certain nutritive values of great importance, but now we are interested in satisfying the needs of a patient who requires less fat and fewer calories, and lacks a taste for low calorie foods.

The second challenge in diet training is to make low calorie foods appetizing and satisfying. Let's look at the egg white. It is not very attractive as is. If we beat this same egg white with others, add a little lemon juice for flavor and stability, some marmalade and some sugar,

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and pour it into a double boiler where it can steam for an hour, we'll have a low calorie dessert soufflé that is dramatic and appealing, and with new satisfying bulk. We'll watch that steam.

But "Let them eat soufflé" is no over-all answer to simplified diet planning—back to the whole egg.

There are 77 calories in this shell. Break the egg into a ramekin, season it—add herbs if you like, set it in the oven, bake for 15 minutes—and it still has only 77 calories. Fry it in butter, and it adds up to about 125 calories. Beat it up with a little milk or cream, then scramble it in butter, and you have run the total up to about 175 calories. Make it into a cheese omelet, and you have 275 calories. At that, you are likely to want a two-egg omelet: score, 350 calories. Eat it with 2 strips of bacon and the 77 calorie egg is part of a 450 calorie dish. But if you ask your patient what he has for breakfast, he'll say, "Oh, juice, an egg, sometimes two. . . ." Patients need to be made aware of the calorie cost of added ingredients in cooking and serving.

The ideal preliminary to any discussion of weight control would be to sit down to a meal with your patient. You would soon find out how the extra calories are sopped up. I cannot resist confessing that I have enjoyed lunching with some of you, and sometimes come away noting mentally that extra herring in cream sauce may be why Dr. Y's waistline isn't what it used to be. Or that Dr. Z may recognize that a martini and a fruit dessert about balance out, but his over-all caloric needs aren't what they were 10 years ago. I note this not out of shrewishness, but because your understanding of patients' problems is basic to helping them to a simpler method of weight control. I happen to like herring in cream sauce and enjoy a martini, too. This is why I welcome the end of the Diet Decade—the end of the crash, boom, overnight, week-end, on-again, off-again diets, and the beginning of weight control based on normal meal patterns.

There is no doubt that Americans really think about weighing less. The magic letters d-i-e-t on a magazine or newspaper run newsstand sales up automatically. And when one diet fails, your patients, and our readers, rush out to buy, try—and discard—another. I have written 41 diets in the past 10 years, each carefully calculated and medically approved. I am now convinced that no diet can succeed if it cuts food too far below the calorie level which must be the patient's permanent pattern. Temporary diets cannot create a consistent pattern of eating.

We have mass-produced diets in the United States. This might, at first glance, seem a simplification. The patient is weighed-in, examined, you have a brief discussion, decide how many calories he needs, and hand him—or her—printed menus for a day, a week, or a month. We do not, however, have mass-produced appetites.

I have designed a diet based on the taste of a leading model, as sophisticated in her eating habits as in her bony structure. She enjoys steak tartare (and appreciated the suggestion that for chopped raw beef, she use round steak, the lowest calorie cut of all). She also enjoys steamed artichokes and consented to dip them in lemon juice instead of butter. But housewives, even status seekers, don't regularly lunch on artichokes. A typical housewife rejected three complete diet menus because they included breakfast patterns other than those to which she was accustomed. When she found a day's menus beginning with orange juice, egg, toast with butter, and coffee, she was on the road to complete acceptance of the diet menu. Make it a special point to ask patients whether they understand and accept *all* the foods indicated on any menu, and all the methods of preparation.

For true simplification of diet planning, don't try to impose an alien way of eating. Instead, keep as close as possible to the patient's own meal pattern, eliminating some foods and altering where necessary to correct nutritional levels and conform to his caloric needs.

It is fairly quick work to establish how much a patient is overeating. If he has gained 10 pounds in the last year, he has managed to consume 35,000 calories more than he needs, or more than his body uses up. It may be that he acquired a power lawn mower instead of a hand model, or a second car, so that he drives to the station instead of walking. Or perhaps he has reached one of the plateaus at which it is necessary for each of us to *reduce* our calorie intake by about 10 per cent to prevent weight gain. Or he may unthinkingly absorb 100 extra calories a day—in a snack at a coffee break, or by nibbling on a new savory, or just in helping himself to an extra pat of butter, or extra gravy.

If the patient who puts on 10 pounds in a year were to cut his calories by just 100 a day (or if you catch him at 5 pounds, and he cuts 50 calories a day) he will stop gaining and take off the extra pounds he carries. Dr. Pollack calls this the module principle of weight reduction, because like build-it-yourself furniture, it enables you to construct a sound diet pattern from small, dovetailed units. Tackling the module,

or unit of reduction necessary to bring meals into calorie balance for the patient, is far simpler, saner and sounder than trying to substitute a completely new eating pattern for one which may have deeper roots than we can untwine.

To establish a module for reduction, or the number of calories a patient must cut in order to avoid gaining weight,

First: Establish the number of pounds gained since the last weighing-in, or since the patient was at what he considers optimum weight.

Second: Multiply this by 3,500, the number of excess calories which contribute one pound of weight.

Third: Divide by the number of days in which this weight was gained.

Fourth: Subtract that number of calories *per day* from the patient's diet, and you have established his module of calorie reduction, and the level at which he will maintain normal weight.

Some researchers have questioned whether, with contemporary patterns of living requiring as little activity as they do, it will be possible for us to maintain normal weight levels without a starvation diet.

In determining what could be the base diet below which a module for reduction should not go, we studied the calorie cost of a base diet designed to meet the daily food requirements as outlined in four basic food groups of the U.S.D.A. and the standards of the National Research Council. It is possible to meet these needs with carefully selected menus at as few as 1,000 calories a day. It is easy to do this at 1200 to 1400 calories a day. For example, you can eat as follows, at 1,000 calories:

Base Diet—1,000 calories to meet needs for women and small men while reducing.

BREAKFAST

1 medium orange
1 egg baked, poached or boiled
1 slice whole wheat toast
coffee or tea, plain
1 cup skim milk (8 oz.)

LUNCH

Sandwich of:
¼ cup tuna fish, drained
¼ cup cole slaw
2 slices enriched bread
⅓ cup fresh strawberries
coffee or tea, plain

DINNER

3 oz. broiled calves' liver
¾ cup steamed green beans
1 boiled new potato
1 slice rye bread
½ pat butter
¼ cup cottage cheese with
½ cup diced melon
coffee, tea or water

SNACK

1 cup skim milk

Substitute whole milk for skim milk, and this diet still comes to under 1200 calories. The nutritive essentials can be had at about one-half the over-all calorie needs of the average woman or man. I describe the 1,000 calorie diet in detail not to suggest another drastic reduce-fast diet, but to indicate the large areas of choice from which we add calories and food values to our menus. Let us look now at how these menus may be expanded, first for a woman, at 2000 calories:

BREAKFAST
1 medium orange
1 egg baked, poached or boiled
1 breakfast sausage (1 oz.)
1 slice whole wheat toast
½ pat butter or 1 tsp. sugar for beverage
coffee or tea, plain
1 cup whole milk

LUNCH
1 cup vegetable soup
Sandwich of:
½ cup tuna fish, drained
1 tbsp. mayonnaise or oil
¼ cup cole slaw
2 slices enriched bread
100 cal. dessert or 50 cal. dessert and cream and sugar for coffee or tea

DINNER
4 oz. broiled calves' liver
¾ cup steamed green beans
2 boiled new potatoes
tossed green salad with
1 tbsp. blue cheese dressing
1 slice rye bread
1 pat butter
1 scoop ice cream with
½ cup diced melon
coffee or tea

SNACK
1 cup whole milk
1 graham cracker

Next, for a man, at 3,000 calories.

BREAKFAST
1 medium orange
2 eggs, scrambled with
½ pat butter
2 breakfast sausages
2 slices whole wheat toast
1 pat butter
1 tsp. sugar with tbsp. light cream for coffee or tea
1 cup whole milk

LUNCH
1 cup vegetable soup
2 soda crackers
Sandwich of:
¾ cup tuna fish, drained
1 tbsp. mayonnaise or oil
¼ cup cole slaw
2 slices enriched bread
1 pat butter.
150 cal. dessert
cream and sugar for coffee or tea

DINNER
1 whiskey and soda or a juice
5 oz. broiled calves' liver
2 tbsp. browned onion slices
¾ cup steamed green beans
3 boiled new potatoes
tossed green salad with
1 tbsp. blue cheese dressing
2 slices rye bread
2 pats butter
1 scoop ice cream with
½ cup diced melon
cream and sugar for coffee or tea

SNACK
1 cup whole milk
2 graham crackers

You will note that these calorie levels are somewhat lower than those listed as average by the National Research Council charts, which are based on Metropolitan Life Insurance Company statistics now some decades old. As menu-makers, we are bricklayers in an area where physicians and the researchers are the architects and engineers of diet planning. But from our observation, I am convinced that in terms of current energy needs, and current social mores, there is a need for re-calculation of both the daily recommended caloric intake for average men and women, and of the tables of average heights and weights.

It is my strong suspicion that many contemporary women would consider themselves too heavy if they ate 2,300 calories a day. Even 2,000 calories a day are too much for some women under 5′ 2″.

Where to cut the 2,000 calorie menu? First, the mayonnaise from that lunchtime sandwich; next, if necessary, one dessert. Why not give up the sausage at breakfast? Possible . . . but that extra treat helps give satiety all morning. The soup at lunch could go, but it is good to sip while the sandwich is being prepared.

On the man's side, that whiskey and soda might be technically the soundest reduction. But our man is no technician, so let's give up 1 dessert, or 2 pats of butter—or, if necessary, both.

This brings us to the art of surrender, or how to relax and enjoy the inevitable when it becomes necessary to cut back a measured amount in each day's food. You might suggest these Ten Commandments for Weight Control:

1. Retain the basic foods: 2 servings of meat, poultry or fish a day; 4 servings of fruits and vegetables, one of them a citrus fruit; 4 servings of bread or cereal; 2 cups of milk or equivalent milk foods, for adults.

2. Eliminate a food you feel you can do without; preferably a fat or sweet, in the number of calories which make your daily module for reduction.

3. Please yourself by adding a luxury touch to your meals in table-setting and in foods not high in calories: mushrooms to dress your meat, strawberries or cantaloupe to round out a dessert.

4. Don't skip meals; it is easier to avoid overeating if you are not over-hungry. Keep on hand the low calorie foods which you may nibble freely: icy cold carrot sticks, celery sticks, raw mushrooms, clear consommé, pickles, fennel—the choice is wide. Any low calorie food may be made more interesting with a wide choice of herbs.

5. Slice foods very thinly. Three ounces of London Broil looks like twice as much on the plate as 3 ounces of solid sirloin steak.

6. Eat very slowly.

7. Really taste, savor fully, everything you eat. (At women's club talks, I borrow a cream puff from the refreshment table and taste it. Then I describe the flavor of that bite fully: the pastry is so short it shatters in a thousand pieces on my tongue. The filling is mocha, with a dash, really just a nuance, of nutmeg. The frosting—ah, that is Swiss-semi-sweet chocolate, and yes, they've added just a trace of coffee for a mocha tang. And now, having tasted, really savored that cream puff—I've had it.) Become a gourmet, not a gourmand.

8. Use a smaller plate to serve a calorie-reduced portion. The food will look like more.

9. Don't try to live completely without the satiety foods. Potatoes, bread, a moderate amount of fats and sweets help you stay on a sane diet, without cheating. Learn to eat them in lower calorie ways. One-half a boiled potato is 50 calories—no cost for a parsley sprinkling. That same half potato (63 grams) sliced and French fried, adds up to 235 calories. Sliced, sprinkled with paprika and broiled, it is again only 50 calories, and has the color and appetite appeal reminiscent of French fried potatoes.

10. Whatever calorie reductions are necessary, *remember that they are for forever*. You can only lessen the calories you regularly eat as you grow older—never increase them. On a consistently calorie-adjusted diet, a very occasional binge doesn't hurt. It's good for the soul.

These Ten Commandments may make it simpler for your patient to live with a reduced calorie count. Tackling the margin of a patient's overeating, and tackling that margin wherever possible within the first year of weight gain, simplifies diet planning to prevent obesity.

Building a pattern of conscious, rigid rejection of a small portion of high calorie foods each day, establishes a pattern of consistent weight control. Increasing the daily portion or module of rejection, and if possible increasing daily physical activity, prevents the gradual increases in girth which some previous generations and other cultures accepted as normal, but which we recognize as dangerous, to say nothing of being unesthetic.

After a decade of diets, Americans are conditioned to the need for consistent prevention of obesity, but not quite strong enough to stick

to rigid imposed diets. It is far simpler to measure, and control, 100 to 200 calories of *reduction* each day, than to count 1200 to 1800 calories of complete diet menus.

You can establish more successful modules for reduction if you orient your diet discussion to the current meal interests of patients, and include in the diet plan foods which have contemporary appeal.

In the long run, you can't prescribe a better exercise than the old reliable of moving the head from right to left when food is offered, or a better simplification of diet planning than the two words, "Eat Less".

Since the "less" that is eaten should be taken from high fat, high calorie foods, a sensitive awareness of current tastes, a projection of your own pleasures in eating, a bit of "Let them eat soufflé" is important. And if you'd like to try it, we'll have some waiting, ready at the end of the program.

THE GLORNEY-RAISBECK FELLOWSHIP IN THE MEDICAL SCIENCES

The Glorney-Raisbeck Fellowship in the Medical Sciences will be awarded by the Committee on Medical Education of The New York Academy of Medicine for one year of research and/or study in any field of medicine or its allied sciences. The initial award will be for the academic year beginning July 1, 1961. Under circumstances deemed appropriate by the Committee, the Fellowship is renewable on a year-to-year basis for two additional years.

The Fellowship, which carries a stipend of $5000, is open only to holders of the M.D. degree who have demonstrated potential for productivity in research and teaching. In general, preference will be given to physicians from the Greater New York area.

A candidate should be prepared to give assurance that he will have an institutional appointment which will enable him to carry out the objectives of his program of research and/or study. Such institutions will be encouraged to supplement the Fellowship stipend. Candidates also should be prepared to be interviewed by the Committee (out-of-town candidates at own expense).

Deadline for receipt of applications is *SEPTEMBER 1, 1960.*

Requests for application forms and additional information should be addressed to:

AIMS C. MCGUINNESS, M.D.
Executive Secretary
Committee on Medical Education
The New York Academy of Medicine
2 East 103 Street, New York 29, N. Y.

Symposium on

PREVENTION OF OBESITY*

SUMMARY OF REPORTS

W. H. SEBRELL, JR.

Director, Institute of Nutrition Sciences, Columbia University, New York, N. Y.

IT is a great pleasure for me to participate in this program because I am firmly convinced that, from a public health viewpoint, it is the prevention of obesity to which we should give our attention, rather than continuing to concentrate on the treatment of obesity, as most of us have in recent years.

As with any disease or public health problem, it is always better to prevent it than to have to deal with it after it has developed. So this meeting to deal with the prevention of obesity interests me greatly and is a subject to which we need to give much more attention. One of the reasons it has not been given more attention is that we have not had a sufficient understanding of the problem. This has been an outstanding Conference. Some interesting and important data have been presented, different viewpoints have been expounded, and from the new material submitted here I believe we can lay the foundations for a health program in the prevention of obesity.

*Dr. Powdermaker*** gave an interesting summary of the anthropological approach to the problem. She pointed out the attitudes toward food in primitive societies where food gathering is one of the important activities of life, in which most of the primitive civilization is engaged and where food shortages are of the utmost importance, in contrast to the plenty of modern society in the Western World with its decrease in physical activity, and in the midst of which we are becoming more conscious of obesity. This consciousness of obesity goes along with an

* Presented at the conclusion of a *Symposium on the Prevention of Obesity*, sponsored by the American Heart Association and held at The New York Academy of Medicine, May 26, 1959.

** See *Symposium on Prevention of Obesity, Part I.* Powdermaker, H. An anthropological approach to the problem of obesity, *Bull. N. Y. Acad. Med. 36*:286-95, May, 1960.

overturning of everything that overeating has stood for in the past. We have a change in our standards of beauty but not in our standards of man. It was not so very long ago that the cartoonists' emblem of success and prosperity was the man with a big gold watch chain hung across a large paunch. The destruction of this emblem and all it means is certainly a psychological factor of some consideration.

Dr. Powdermaker pointed out the social importance of our dinner parties and the changes that are going on as they reflect the individual style and taste in cooking, and how we tend more and more to become gourmets. She did not mention it, but as she was talking, I thought of the current fad for outdoor cooking, which is a reflection of individual style. In the midst of all this, parents are still the givers of food to children. Good eating still produces a euphoria and the eating of food still remains a symbol of love, affection and friendliness. So that we have an increasing opportunity to overeat and become obese while our knowledge of food and obesity introduces conflicting ideas. It is clear that problems in social anthropology are important factors in obesity. It is not clear just exactly what we are going to do about them. We all know that the early establishment of food habits, good or bad, is a very basic thing that is difficult to change, but we must have a better understanding of the proper way in which to change food habits.

*Mr. Herbert Marks** presented and discussed the questions: "Why should we be concerned about obesity? What are the health problems of obesity?" He told us of the importance of obesity in relation to health. He stressed particularly the relationship to heart disease, mentioning the fact that a white man of age 25 has 16 out of 100 chances of dying of heart disease while the chances are 30 in 100 for all other diseases.

He indicated that the figures on mortality are more satisfactory than those on morbidity for evaluating the effects of obesity on health, and he cited the extensive life insurance data which indicate that even a moderate amount of overweight is associated with an increased mortality, which increases with the degree of overweight. He made the interesting point that a study of currently available data now indicates that the previously assumed advantage of moderate overweight in young persons is no longer true. When I was a medical student, I was taught

* See *Symposium on Prevention of Obesity, Part I.* Marks, H. H. Influence of obesity on morbidity and mortality, *Bull. N. Y. Acad. Med.* 36:296-312, May, 1960.

that it was advantageous for adolescents to be a little overweight, that it was better to be overweight when you were young, and underweight when you were older. This is no longer true because, when the reduction in mortality from tuberculosis and pneumonia is taken into account, even this apparent advantage of slight overweight in the young disappears. In the overweight mortality is significantly elevated at all ages, compared with optimal weight mortality, with ratios up to age 50 on the order of 200 per cent.

In relation to specific diseases, he mentioned how important obesity is in diabetes, where the excess mortality is about four times that of standard risks. He paid special attention to the studies that show that there is a relation between overweight and elevated blood pressure, angina pectoris, ischemic heart disease, liver disorders, gall bladder disease, osteoarthritis, and even malignancy of the endometrium and the biliary tract, although there is no apparent relation to other malignant conditions.

He then turned to the interesting question of whether, from a health viewpoint, if one is already obese, it would pay to reduce. In answering this question he mentioned the studies that show that elevated blood pressure falls when weight is reduced, and that mortality statistics improve. So it *is* desirable to achieve weight reduction because it may be followed by improved health in the overweight individual with serious disorders.

Therefore, I think we can summarize Mr. Marks' viewpoint by saying that his remarks emphasized the great importance of the *prevention* of obesity in order to avoid increased health hazards.

*Dr. Hartroft** discussed the pathology of obesity, and pointed out the various *pathological* obese states, which have not thrown much light on the normal mechanism of storage of fat. He observed that at one time obesity was considered a sign of health, vigor, beauty, respectability, wealth, and trustworthiness. These words are of considerable importance in a real attack on the prevention of obesity.

He stressed that adipose tissue is a normal special organ with the specific function of storing fat, and it is only the excessive storage of fat that becomes a problem. He mentioned the fusion of the adipose tissue cells, and pointed out that in fatty degeneration, the fat in the cells is

* See *Symposium on Prevention of Obesity, Part I.* Hartroft, W. S. The pathology of obesity, *Bull. N. Y. Acad. Med. 36*:313-22, May, 1960.

not necessarily related to obesity. This kind of fatty degeneration may occur in starvation. He told us about the experimental production of obesity in animals by various methods such as insulin injection, or hypothalamic damage. He pointed out that in this type of fatty disease or abnormality the fatty liver of obesity is different from that caused by a lipotropic deficiency, such as choline, while the fat in the liver in starvation and in diabetic animals resembles that seen in obesity.

He presented us with some autopsy data that might superficially appear to be at variance with some of the conclusions that Mr. Marks made. Dr. Hartroft's data fail to show an association between hypertension, myocardial infarction and obesity in non-diabetic adults.

I do not necessarily see any conflict between Dr. Hartroft's findings at autopsy and Mr. Marks' findings based on life insurance data. I have no doubt that they are both correct. They are dealing with widely differing situations, differing types of data, differing material, and there is probably some satisfactory explanation to reconcile both of these findings. Dr. Hartroft did agree that extreme obesity is undesirable from the standpoint of public health and preventive medicine—so there is no difference of opinion on this point.

*Dr. Mayer** presented an extremely interesting and stimulating report. He went to the heart of the problem immediately by asking the questions, "Why do people over-eat?" and "Why do some people take in more energy than they expend?" And he mentioned that, because of over-simplification of the problem and a superficial viewpoint, there has of late been a tendency to transfer obesity from the category of a serious medical problem to that of being a moral problem.** We all agree, I think, with Dr. Mayer's viewpoint, that it is the interaction of heredity and environment that makes us what we are.

Dr. Mayer showed that overeating is due to the interaction of factors between the host on one hand, that is, genetic factors, and the agent, such as trauma or hormones or chemicals; or, on the other hand, environment as reflected by exercise, the nature of the diet and social and cultural factors. He pointed out the several types of genetic obesity that are known to occur in experimental animals and spoke at length about hereditary hyperglycemic obesity in experimental animals.

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* See *Symposium on Prevention of Obesity, Part I.* Mayer, J. Genetic factors in obesity, *Bull. N. Y. Acad. Med.* 36:323-43, May, 1960.

**In the sense that excessive food intake is comparable with alcoholism as a moral and social problem.—Ed.

I was particularly interested in his remarks about children and the differentiation between metabolic obesity and regulatory obesity—the establishment of a method of distinguishing between these two types would be exceedingly important and useful.

His conclusions were: 1) we must understand normal physiology better; 2) in order to treat obesity we must understand the primary abnormality; and 3) we should not fear genetic factors.

I certainly agree with all of the above-mentioned points. There are many hereditary conditions influenced by genetic factors which have been successfully attacked in the past. It would be a mistake to ignore genetic factors in obesity. It is true that from a long-range viewpoint most of our efforts at weight-control have been failures. Obese people can and do reduce temporarily, but studies over the years indicate that they usually revert to their previous obese state.

Dr. Buskirk talked about the basis for calculating energy needs. He mentioned our energy needs, our energy intake, and the measurement of energy expenditure. He spoke of the modern research equipment that is being used to study metabolism, including miniaturization and telemetering, which will make these measurements more precise. He pointed out that the caloric cost of living becomes less, the greater the use of power in many occupations,—and changes in the way we spend our day have their effects on energy expenditure.

He raised the question of our daily variation in energy expenditure, observing that it fluctuated greatly, and he made quite a point of week-end activities. I was impressed with the great decrease in calorie expenditure in a man who spent his week-end lying down, compared with an increase up to three times with vigorous exercisers.

He indicated the daily heat production on equi-caloric diets of different protein content, showing that there was no difference in one pair of subjects and a moderate increase with high protein in another pair, indicating that the specific dynamic action depends more on the total diet than on just the protein content. He spoke about the caloric cost of transporting the body around, and mentioned the gain in weight in man as he becomes older, largely due to fat deposits. He pointed out the variation in the calorie expenditures in different occupations, varying from 2,800 a day for clerks to over 5,000 a day for a man dog-sledging.

As Dr. Buskirk indicated, we need better information about what we are actually doing, and the caloric cost involved. I was impressed

with the difficulties of being precise in this type of measurement on an individual. Fortunately, from a health viewpoint, we don't have to be this precise in order to tackle the problem of the prevention of obesity.

The kind of information that Dr. Buskirk and his group are collecting is essential for a complete understanding of the problem. These studies will yield us a great deal of very valuable information, but meanwhile we can go ahead with our program of prevention of obesity while they are obtaining this additional information.

In his discussion of the prophylaxis of obesity, *Dr. Pollack* pointed out that we gain weight as we get older as a result of a continuing intake of calories slightly in excess of those that we expend, due to our decreasing activity, and without an increased intake. This was one of the important points in his presentation. We establish certain patterns of eating when we are young adults; or in adolescence, we become accustomed to a certain food intake. We don't realize that we should reduce our food intake as we get older. We continue the same caloric intake year after year, while our activity decreases and our weight gradually increases, because our basal metabolic requirements per unit of body weight continue to decrease with age.

We noticed from his data that just a tiny decrease of 15 calories a day in a hypothetical man made a considerable difference in weight with advancing age, and resulted in a reduction in weight from 175 lbs. to about 160 lbs. between the ages of 40 and 60 years.

Dr. Pollack mentioned the basic point that there are only two ways to prevent obesity. One is to decrease the food intake and the other is to increase the caloric expenditure. It's the little things that count, and prevention means equilibrium. It is neither necessary to take a seriously deficient diet, nor to restrict oneself very severely nor to use the deficient diet needed for treatment. *In prevention*, it is just equilibrium between food and work. This is very simple to do and does not require any serious restriction in food.

Dr. Pollack also pointed out the basic need for watching the scale over a long period of time. He noted, too, how rapid changes in water balance disturb people. Body weight must be watched week after week. It is the slow steady gain that is serious but which requires only a slight adjustment in calories for correction.

Finally, *Miss Schur* covered a number of very fundamental points in her paper—on teaching the individual about diet. The prevention of

obesity is largely a problem in health education, and she pointed out remarkably well the basic things involved in such an educational program. The first point is to identify the high calorie and the low calorie foods for the individual; this can be done fairly easily. Secondly, make the low calorie foods appetizing and satisfying. And thirdly, base the weight control on a normal meal pattern—no crash diets, no temporary diets, but instead, establish a consistent pattern of eating.

One of the fundamental points of such a program is that the diet must be based on the taste and food likes of the individual. That is why it is so difficult to succeed with a printed diet sheet, because one should talk directly with the patient, keeping as closely as possible to the individual's normal meal pattern; making as little change as possible in what the individual likes and what the individual is accustomed to eating —and bearing in mind that only small changes need be made. If one is concerned with prevention and not treatment, then it is necessary to reduce the intake by only 50 calories a day. This is quite easily done.

Miss Schur gave us ten commandments for patients to follow, and I was much interested in the psychological approaches she used, especially her deliberate tasting approach to a cream puff—of making a little bit of food look like a lot, of making unattractive food appear attractive, of making low calorie food look and taste like high calorie food, and the need to eat slowly—all reflect the need for self-control and strong motivation which are basic factors in the prevention of obesity. Most important of all is the dictum that these changes in dietary habits are for a *lifetime*. This is not only a diet, it is a new way of life brought about by slight changes, a way of life that can pay dividends in years of greater activity and better health.

A program for the prevention of obesity should really begin with school children or with the parents of small children.

Dr. Mayer mentioned the obese children of obese parents—we don't really know how much of this is due to heredity and how much of it is due to bad food habits passed on by parents to children at an early age. Experimental animals become obese if they are given a high fat diet at a very early age. So the problem, or a large part of it, is to establish proper food habits early in life in order to *prevent* the occurrence of obesity in later years.

Prevention of obesity is one of our biggest and most difficult health problems both now and in the future, if we are to make greater prog-

ress in our battle against the degenerative diseases. People now live longer with the help of antibiotics and immunizations, but the greatest progress in saving of life has been in *young people*. We have made *relatively little* progress at the other end of life, in prolonging the useful years of aged individuals. We have not made nearly as much progress with those diseases which are known so well as the top killers, the greatest of which is cardiovascular disease—which is partly the result of a lifetime of wrong habits of many kinds, including those associated with food.

The prevention of obesity should stand high on the list of health programs in order to make the best progress in controlling our health problems of the future.

NOTICE TO FELLOWS PLANNING TO VISIT ENGLAND

Fellows of the Academy are reminded that reciprocity exists between the Royal Society of Medicine, 1 Wimpole Street, London, England, and the Academy.

The members of each group are cordially invited to avail themselves of the hospitality and assistance of the other institution. Fellows of The Academy of Medicine who plan to visit London are urged to take advantage of this arrangement, and letters of introduction may be secured on request from the Director of The Academy.

In addition, Fellows of The Academy who are interested in becoming "affiliate members" of the Royal Society of Medicine may obtain appropriate application forms from The Executive Secretary, Committee on Medical Education, The New York Academy of Medicine.

NEW YORK PATHOLOGICAL SOCIETY

ABSTRACT OF PAPER AND DISCUSSION

Presented at the Anniversary Meeting on January 22, 1959, at The New York Academy of Medicine

Degradation of Radioactively Labeled Proteins in Patients with Cancer

STUART W. LIPPINCOTT

Brookhaven National Laboratory

Abstract of this paper and discussion by Samuel Korman, Montefiore Hospital, are not available

*Virus Etiology of Cancer**

ROBERT C. MELLORS

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In a substantial proportion of rabbits bearing Shope papillomas, there is a progression of growth from papilloma to invasive, and even metastasizing, carcinoma, as shown by the work of Rous and Beard[1] and Kidd and Rous[2]. These workers were able to transplant some of the papilloma-derived carcinomas to rabbits, and, in so doing, observed that for many transplant-generations grafts of these carcinomas had the power to immunize the recipient animal against Shope papilloma virus[3-5]. This finding, together with the recoverability of Shope papilloma virus in cell-free extracts of such carcinomas under special conditions, indicated that the virus was present in the papilloma-derived carcinomas, at least for a while. In one line of transplantable carcinoma, the Vx2 carcinoma, the power to immunize against the papilloma virus was lost after more than eight years of propagation[5], equivalent to 46 generations of transplantation; while in another, the Vx7 carcinoma, the power to immunize was still retained after more than 46 generations of transplantation. Dr. Rous kindly made both of these transplantable carcinomas available for study with fluorescent antibody for the cellular localization of Shope papilloma virus. No Shope viral antigens were detectable with fluorescent antibody in the Vx2 carcinoma; however, in the Vx7 carcinoma, grafts of which still immunized against Shope virus, viral antigens were detected in nuclear sites, as in the cottontail papilloma[6, 7], but in cancer-cell nuclei much altered by the presence of the virus.

The next sequence of sections of the Vx7 carcinoma will be projected in pairs showing the identical field stained with hematoxylin-eosin and stained with the direct fluorescent antibody method for Shope viral antigens. This is a field of Vx7 carcinoma cells whose nuclei for the most part are large and contain a fine network and coarser clumps of blue-stained chromatin. The two cells in the center of the field contain pyknotic dark-blue nuclei, and the cytoplasm which appears to be shared by the two cells is dark red. This is the corresponding fluorescent antibody stain. Shope viral antigens, shown by the white areas, are detectable only in the two Vx7 carcinoma cells in the center of the field, and these sites of localized virus correspond to the pyknotic dark-blue nuclei.

This is a field of Vx7 carcinoma cells (slide). One round nuclear mass in the center of the field has a deep purple color, a mixture of blue and red. This is the corresponding fluorescent antibody stain. Shope viral antigens are detectable only in the

* This work was supported by grants from the National Cancer Institute of the National Institutes of Health, Public Health Service, and by grants from the Damon Runyon Memorial Fund.

round body in the center of the field which corresponds to the nucleus with deep purple color.

This is a field of Vx7 carcinoma cells. Arrows point to nuclei of several kinds: blue nucleus with a trace of purple, purple nucleus, and red nucleus, as well as a nucleus which contains a tiny round, purple and red inclusion. As you will soon see, each of these nuclei, but none of their neighbors, contains Shope viral antigens. It is clear then that there is considerable variation in the nuclear morphology of cells which contain virus. This is the corresponding fluorescent antibody stain (although at about double magnification). This site of viral antigen corresponds to the blue nucleus with a trace of purple, this to the purple nucleus, this to the red nucleus, and this to the nucleus with a purple and red inclusion.

This is a nucleus of Vx7 carcinoma cell at high magnification, stained with fluorescent antibody for Shope viral antigens which are distributed in a fine network and coarse clumps apparently corresponding to the fine and the coarse distribution of nuclear chromatin in this cell.

Now what do these observations suggest regarding the interaction of virus and infected cell during the process of oncogenesis? In the cottontail papilloma[6, 7], Shope viral antigens were not detectable in the proliferating epithelial cells, that is, in those cells in which virus would most likely be present were it to carry out a role as a growth-promoting agent. Viral antigens were demonstrable, however, in the keratinized and non-viable epithelial cells, where the presence of the virus would have no apparent influence on the growth of the papilloma. In the Vx7 carcinoma, viral antigens were detectable in nuclear sites which corresponded variously to chromatin, to nuclear sap, and to small and, ultimately, large eosinophilic nuclear inclusions. The nuclear chromatin of the virus-infected cell appeared to be gradually replaced by eosinophilic protein material which became rich in its content of viral antigens demonstrable by fluorescent antibody and relatively poor in its content of deoxyribonucleic acid, as shown by diminished staining both with hematoxylin and with the Feulgen reaction. It is possible that the virus itself undergoes similar changes in composition, in the early stages of development existing in the proliferating cells of the Shope papilloma and of the Vx7 carcinoma as incomplete virus, rich in content of deoxyribonucleic acid and poor in content of protein and therefore not stained with fluorescent antibody; and in the later stages of development increasing in relative content of protein demonstrable with fluorescent antibody, a condition which prevails in the keratinizing layer of the Shope papilloma and in a relatively small proportion of the Vx7 carcinoma cells.

In this view, the incomplete virus may be considered, at the risk of over-simplification, as essentially a deoxyribonucleic acid core which is intimately associated with nuclear chromatin, passes from cell to cell in mitosis, and in this manner is protected from inactivation by circulating antibody or other extracellular factor. The incomplete virus is not recoverable in cell-free extract as a transmissible infective agent and is by all present means of study not detectable in the cell as an extrinsic agent. However, in a later stage the development of the virus is completed by the acquisition of a protein shell or skin about the deoxyribonucleic acid core. The protein shell is the serologically active component of the virus, protects the nucleic acid core, serves to preserve the transmissibility of the virus to a new host or the laboratory recoverability of infective virus in cell-free filtrates, and is a determinant by surface interaction of the specific cellular affinities of the virus on inoculation into a new host. Can it be possible that the generality of neoplasms is caused by viruses which for the most part exist in an incomplete stage of development, are therefore indistinguishable by present means of detection from an intrinsic cellular factor, and only rarely declare their presence by becoming complete and acquiring the attributes which led to their identification as extrinsic agents? Further work in support or denial of such an hypothesis is clearly much needed.

REFERENCES

1. Rous, P. and Beard, J. W. Progression to carcinoma of virus-induced rabbit papillomas (Shope), *J. exp. Med.* *62*:523-48, 1935.
2. Kidd, J. G. and Rous, P. Transplantable rabbit carcinoma originating in a virus-induced papilloma and containing the virus in masked or

altered form, *J. exp. Med. 71*:813-38, 1940.
3. Kidd, J. G. Enduring partnership of a neoplastic virus and carcinoma cells, *J. exp. Med. 75*:7-20, 1942.
4. Kidd, J. G., Beard, J. W. and Rous, P. Serological reactions with a virus causing rabbit papillomas which became cancerous. I. Tests of the blood of animals carrying the papilloma, *J. exp. Med. 64*:63-77, 1936.
5. Rous, P., Kidd, J. G. and Smith, W. E. Experiments on the cause of the rabbit carcinomas derived from virus-induced papillomas. II. Loss by the Vx2 carcinoma of the power to immunize hosts against the papilloma virus, *J. exp. Med. 96*:159-74, 1952.
6. Noyes, W. F. and Mellors, R. C. Fluorescent antibody detection of the antigens of the Shope papilloma virus in papillomas of the wild and domestic rabbit, *J. exp. Med. 106*: 555-62, 1957.
7. Mellors, R. C. Viruses, genes, and cancer, *Fed. Proc. 17*:714-23, 1958.

DISCUSSION

PEYTON ROUS: I ask you, Dr. Kidd, to supply my deficiencies in thought and to fill in such facts as I will undoubtedly leave out.

Dr. Mellors' findings are most exciting and, when taken in conjunction with his previous work, they open vistas for the future, as also a rather dismal look into the past: for they show how preconceptions can hamper experimentation. Until Dr. Noyes and Dr. Mellors found that the active tissue of Shope papillomas contains almost no viral antigen demonstrable by the fluorescence method, workers on the growth had assumed that this tissue would yield most virus and hence had worked with it mainly, discarding the keratinized material. If Dr. Shope were here I would congratulate him on the way in which, without any preconceptions whatever, he has always preserved in its entirety papilloma tissue taken for virus, making vertical cuts through the growths, and thus obtaining representative chunks for glycerination. More than this, when he gives out the chunks for extraction of their virus he doesn't say whether to make any selection from their tissue.

There is no need to tell you what an obstinate material keratin is. I have tried many times in the past to dissolve that of the Shope papilloma in ways whereby one might release a lot of virus and have found none that didn't destroy this. Even to keep living papilloma free of keratin by means of depilatories with the aim of noting the first signs of the secondary cancers arising in such growths is a most tedious job.

Dr. Noyes cannot be here tonight but he permits me to tell you that he has answered the immediate question raised by his previous joint work with Dr. Mellors,—this being whether the presence of fluorescent antigen in papilloma cells is, or is not, an indicator of the presence of virus in active form. By an ingenious microincineration technique he has destroyed the keratin or the living tissue, whichever he wishes, in slices of fresh papilloma tissue and has tested what is left behind by binding this down on the scarified hyperplastic epidermis of rabbits. Thus he has shown that in the living tissue, where no fluorescence can be seen by Coon's method, no active virus exists, whereas it is present in quantity in the fluorescing, keratinizing tissue. From this one may infer either that the living cells contain non-infective provirus or else too little active virus to give any fluorescence. Dr. Mellors recognizes the possibility that the fluorescence method may be incapable of showing the presence in living cells of tiny quantities of active virus, yet quantities not too tiny to render them tumor cells. Indeed he brought up this matter in a paper presented last spring at the meeting of the Federation of American Societies for Experimental Biology. In this relation Friedewald's demonstration is worth remembering, that under the best of circumstances at least 2000 virus entities per tenth of a c.c. are required to produce a papilloma. How many are necessary to produce fluorescence one does not know.

I turn now to Dr. Mellors' present material, the transplantable cancers arising by secondary change in the virus-infected cells of Shope papillomas. Dr. W. E. Smith, Dr. Rogers and I have succeeded in transplanting 14 out of 16 such cancers by utilizing newborn rabbits as hosts, and six of the seven that were extracted for test yielded papilloma virus, but always in exceedingly small quantity. No virus causing cancer directly was ever got, such as we had hoped to procure. But of necessity we worked with cancers that had arisen in domestic rabbits (since wild ones don't breed in captivity) and even the papillomas of domestic rabbits yield little virus at best, "recoverable virus", as Dr. Shope has called it, and ordinarily none at all. We used recoverable virus to produce the papillomas

from which the cancers derived and recovered it unchanged from these latter. That was the sum of our findings.

Here are lantern slides of the two transplantable cancers most studied by us, so that you can judge the sort of material with which Dr. Mellors worked. You'll note that they differ greatly from the Shope papilloma and that nearly all their cells die before keratinizing, that is to say, at a time when papilloma cells as yet show no virus on fluorescence. The Vx2 carcinoma, which has been propagated for more than 20 years, is completely anaplastic, forming no keratin anywhere, and though in early years its growths carried the papilloma virus or a near antigenic relative, as shown by the fact that their rabbit hosts become immunized against this, in recent years they've induced no such immunity.

Dr. Mellors has worked with the Vx7 carcinoma, a malignant growth not very different from the Vx2 morphologically. It is not completely anaplastic like the Vx2, as the lantern slide shows, but has retained a slight tendency to form papillae and a few of its cells undergo abortive keratinization. It still immunizes against the papilloma virus after more than 40 passages and this virus has repeatedly been recovered from it in small quantity. Large Vx7 tumors consist of a mere shallow rind of living neoplastic tissue, enclosing a great mass of that which has become necrotic, while containing almost no keratin. This being so, one might expect, on the basis of Dr. Noyes' recent negative findings with living tissue of the Shope papilloma, that little if any infective virus would be procurable from it. Yet Dr. Mellors has found individual cells here and there in the living tissue of the Vx7 which glowed brilliantly on the fluorescence test. How is one to explain this? After looking at some of the photographs which he generously showed me two days ago, I went at once to my own Vx7 specimens, stained merely with methylene blue and eosin, to search for cells with eosinophilic cytoplasm and almost pyknotic nucleus such as had fluoresced in his preparations. I found them scattered sparsely throughout the living tissue of the Vx7, notably in areas in which no keratinization whatever had been attempted. They were obviously dying, if not dead, tumor cells, unlike their fellows both in this respect and in their fluorescence. Can it be that some cells more than others of the Vx7 serve so well as a milieu for the multiplication of papilloma virus that they succumb to it as the generality do not, these necrotizing later only because their blood supply is cut off as the tumor enlarges? Is it possible that in the lesions due to relatively simple necrotizing viruses, such as vaccinia, some cells die quickly because overwhelmed by virus, and their neighbors only later as the tissue milieu becomes more pathological?

It seems strange that with so much known of the astonishing phenomena for which the papilloma virus is responsible no adequate study with the electron microscope has been made of this virus in its cellular habitat, in fact, no enlightening study of this sort at all.

ROBERT C. MELLORS: Concerning the detection of viral antigens in healthy-appearing cells, this has been accomplished by other workers using the fluorescent antibody method for the study of other virus-cell systems. But there is some evidence, derived from the study of oncogenic viruses but not limited to this class, that viruses can at times be recovered in higher infectivity titer from a degenerating or dying population of infected cells than from healthy-appearing, infected cells. The detectability of Shope viral antigens in the cottontail papilloma and the Vx7 carcinoma by fluorescent antibody is in accord with this trend. During the last year or so I have undertaken fluorescent antibody studies with Dr. Spencer Munroe of the Rous sarcoma virus in wing tumors of chickens. Viral antigens can be demonstrated in minute quantity in some sarcoma cells which appear morphologically as healthy as their neighbors, although these latter may not contain detectable virus. On the other hand, I obtain the impression that the cells which contain the greatest amount of viral antigens demonstrable with fluorescent antibody commonly show degenerative changes in the cytoplasm and the nucleus; but of the many degenerated sarcoma cells present in a wing tumor, only a relatively small proportion contain viral antigens in detectable quantity.

NEW YORK PATHOLOGICAL SOCIETY

ABSTRACTS OF PAPERS AND DISCUSSION

Presented at the Meeting on February 26, 1959, at The New York Academy of Medicine

*Electron Microscopy of Renal Biopsies**

MARILYN G. FARQUHAR, Ph.D.**

The Rockefeller Institute, New York, N. Y.

The renal glomerulus has been the subject of numerous electron microscopic studies[1]. As a result, many important features of glomerular organization are understood, whereas some others remain in dispute. It has, however, become evident that the precise arrangement of the glomerular components and their basic reactions to disease can be fully resolved only at the electron microscope level. During the past three to four years we have had the opportunity to examine, by light and electron microscopy combined, renal biopsy tissues from patients with a variety of disease processes affecting glomeruli, including lipoid nephrosis, "membranous" glomerulonephritis, acute and chronic glomerulonephritis, amyloidosis, disseminated lupus erythematosus, diabetes mellitus, and pre-eclampsia or eclampsia[2-7]. In this presentation the characteristic features of these glomerular lesions will be described.

For our studies the tissue obtained by biopsy was cut into two segments. One segment was fixed in formalin and embedded in paraffin for examination by light microscopy. The other piece was cut into blocks of less than 1 cu. mm. and prepared for electron microscopy by fixation in buffered osmium tetroxide and embedding in methacrylate[8]. A number of staining methods commonly used to demonstrate glomerular components have been adapted for methacrylate-embedded tissues[9] so that it has been possible to examine contiguous sections by light and electron microscopy.

The components of the normal human glomerulus are: 1) the endothelium with characteristic pores or fenestrations in the peripheral cytoplasm; 2) a basement membrane (ca. 2700 Å thick in adults[10]) which appears virtually homogeneous in the usual osmium-fixed preparations, but shows delicate fibrillar structure after "staining" with lead hydroxide, uranyl acetate or phosphotungstic acid; and 3) the epithelium with its numerous pseudopodia or "foot processes" which interdigitate to cover the entire outer surface of the basement membrane. The only other type of cell we have seen in the glomerulus are smooth muscle cells which enter with the afferent arteriole at the hilus and may follow the primary glomerular capillary branches to some extent.

In children or adults with lipoid nephrosis we have consistently seen[2-4, 7] a pronounced change in the epithelium: loss of the usual foot process organization with a resulting confluence of epithelial cyto-

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** Many of these studies were carried out while the author was Assistant Research Pathologist, University of California School of Medicine, San Francisco, Calif.

plasm along the basement membrane, together with the presence of vacuoles in the epithelial cytoplasm. The occurrence of this lesion in patients with the nephrotic syndrome has also been confirmed by others[11-15]. Differences in the extent of epithelial change are apparent in different patients, but the degree of alteration correlates roughly with the degree of proteinuria[7]. It is evident from examination of serial biopsies in the same patient before and after treatment[7,13] and from studies of aminonucleoside nephrosis in rats[16,17] that the foot process lesion is reversible. The question as to whether this epithelial change is a manifestation of primary epithelial damage in nephrosis or is merely a reaction to underlying basement membrane damage is as yet unsettled.

Recent observations[7] indicate that in patients who do not recover from the initial nephrotic episode(s), eventually progressive (and apparently irreversible) changes occur in the basement membrane. It is particularly significant that the basement membrane damage shows different manifestations in children from adults. (It should be emphasized that loss of epithelial foot processes is seen in both children and adults with "pure" nephrosis and it is only the changes in the basement membrane that differ.) In children the basement membrane undergoes thickening by addition of material which is similar in density and appearance to normal basement membrane. There may also be an accompanying mild endothelial proliferation, deposition of basement membrane-like material between endothelial cells, and (late in the disease process) deposition of fibrinoid. On the other hand, in adults with progressive damage, thickening occurs by addition of a heterogeneous layer to the epithelial side of the basement membrane, giving the epithelial edge of the basement membrane an irregular ruffled contour. The newly-added layer is finely particulate in areas and frequently contains vesicles and other inclusions. The exact nature of the layer is not apparent, and its components and thickness vary greatly from one area to another in the same glomerulus. However, it appears to consist of cytoplasmic components derived from the epithelium together with patches of dense, particulate fibrinoid identical in appearance to that seen in disseminated lupus erythematosus (see below). These basement membrane alterations encountered in adults with nephrosis apparently constitute the so-called "membranous change" (i.e., membranous glomerulonephritis)[18-21]. These lesions are also described and illustrated elsewhere[7].

In classical acute post-streptococcal glomerulonephritis, the well-known cellular, congested condition of glomeruli apparently results from a proliferation of endothelial cells, intraluminal accumulation of leukocytes, and swelling of both endothelial and epithelial cytoplasm, which results in great restriction of both the capillary lumina and urinary spaces. Some deposition of material resembling basement membrane may also occur between endothelial cells. In chronic glomerulonephritis where the progression of the disease has been followed from an episode of acute glomerulonephritis, many of the glomeruli show partial or complete hyalinization which results from the deposition of masses of basement membrane-like material ("hyalin") around the abundant endothelial cells.

In disseminated lupus erythematosus, the most common glomerular changes found on examination of renal biopsies by light microscopy are endothelial proliferation and fibrinoid deposition[22, 5]. By electron microscopy[6, 7] a thickening of the basement membrane is also seen in these patients. Fibrinoid may be recognized by virtue of its characteristic appearance (great density and particulate nature). Much smaller amounts can be identified than can be recognized by light microscopy. The fibrinoid is usually found between the basement membrane and the endothelium (i.e., subendothelial). Sometimes it may also permeate the basement membrane and even accumulate in patches on the epithelial side of the basement membrane. A wire-loop lesion is seen to be composed of a thickened basement membrane together with a broad deposit of fibrinoid.

In diabetes mellitus[8], the earliest manifestation of glomerular disease which can be recognized by electron microscopy is a thick-

ening of the basement membrane. Some increase in basement membrane thickness, up to 10 times normal, is seen in all glomeruli. "Hyalin" resembles basement membrane early in the disease process and frequently is continuous with basement membrane. Later in the disease process, hyalin shows altered staining characteristics and is more heterogeneous by electron microscopy. Hyalin is found between endothelial cells (i.e., interendothelial rather than "intercapillary") and is clearly extracellular, for the endothelial cell membranes can be seen separating it from endothelial cytoplasm. A hyaline nodule differs from the diffuse hyaline accumulations only in the size and shape of the mass, for nodular lesions appear to develop from the diffuse by enlargement of the hyaline masses, as proposed by Bell[18]. Exudative lesions may be readily distinguished from the nodular or diffuse lesions, for they are composed of dense fibrinoid deposits located between the endothelium and basement membrane (subendothelial) in the peripheral glomerular loops. Bergstrand and Bucht[23] have also examined renal biopsies from patients with diabetes mellitus by electron microscopy. They also found thickening of the basement membrane and noted the close association between hyalin and endothelium, but they believed hyalin to be located within endothelial cytoplasm.

In primary amyloidosis[6, 7] a characteristic change in the basement membrane is evident by electron microscopy. The basement membrane shows focal thickenings which may be 20 or more times normal. The thickened areas, which presumably correspond to areas of amyloid deposition seen by light microscopy, are lighter in density than normal basement membrane, and have a loosely-woven, foamy appearance which is quite distinctive from either hyalin or fibrinoid. Similar alterations of the glomerular basement membrane have been reported in a patient with secondary amyloidosis by Geer and associates[24] and in experimental amyloidosis of mice by Miller and Bohle[25]. Spiro[16] describes a fibrous structure in amyloid following staining with phosphotungstic acid.

In pre-eclampsia or eclampsia[6, 7], the most pronounced glomerular change seen by electron microscopy is an extreme swelling of the endothelial cytoplasm. This endothelial swelling results in virtual closing of the capillary lumina and gives rise to a "bloodless" appearance. In addition there are subendothelial and interendothelial fibrinoid deposits in many loops. Biopsies taken after delivery show that the endothelial swelling subsides and the fibrinoid is removed and taken up by the endothelium. Thus, these changes constitute the so-called "reversible" lesions of eclampsia[26].

From studies such as these it is apparent that a greater number of basic reactions of the glomerulus to disease may be recognized at the electron microscope level than can be distinguished by light microscopy. Some of these reactions are distinctive for a given disease process (e.g., the basement membrane change found in amyloidosis). However, most of the changes, such as fibrinoid deposition, hyalin accumulation, basement membrane thickening, etc., are seen in more than one type of disease process. In general, a particular process or combination of processes seems to predominate, resulting in a characteristic pattern for a given disease. It can be hoped that study of these patterns may eventually contribute understanding to the pathogenesis of glomerular diseases.

DISCUSSION

MORRIS F. WIENER: To what extent may etiologic agents be identified by electron microscopy?

MARILYN G. FARQUHAR: Do you mean reactions to particular etiologic agents?

MORRIS F. WIENER: Not the reactions, but rather the morphologic identification of etiologic agents such as bacteria or other particulate organic matter which may provoke or incite a reaction by the renal tissue.

MARILYN G. FARQUHAR: Up to the present, electron microscopy has contributed nothing to the identification of etiologic agents in renal disease.

NORMAN S. COOPER: I would like to ask if the fibrinoid in the lupus glomeruli is completely amorphous electron-microscopically, or does it show periodicity? Also, do you find these changes in lupus patients who had no clinical evidence of kidney disease?

MARILYN G. FARQUHAR: In answer to the first question, the fibrinoid we have encountered has a finely particulate nature. I imagine that what may have prompted you to ask this question is the fact that Pappas, Ross and Thomas[27] have reported fibrillar structure with periodicity in the glomerular fibrinoid found in the generalized Shwartzman phenomenon, suggesting the presence of fibrin and/or fibrinogen. However, two different kinds of fibrinoid have recently been distinguished by immunohistochemical methods[28]: one type, found for example in lupus, is largely composed of gamma globulin, whereas the other type, found in the generalized Shwartzman phenomenon, thrombotic thrombocytopenic purpura, etc., is composed chiefly of fibrinogen.

In answer to your second question, we have indeed seen accumulation of fibrinoid —but usually in smaller amounts—in patients with no clinical evidence of renal damage. The slides which I showed with massive fibrinoid deposits in DLE were from patients with severe renal damage.

MAX WACHSTEIN: I should like to ask Dr. Farquhar two questions. Will you please give your opinion as to whether these various substances, fibrinoid and hyalin, are produced by glomerular cells or rather absorbed from the blood stream, and second, how can one explain the relationship of proteinuria to the foot process changes when, for instance, in eclampsia, proteinuria is usually present, but the foot processes in the slides shown were normal, and, on the other hand, in chronic glomerulonephritis, usually proteinuria disappears or is, at least, considerably diminished and the foot processes remain?

MARILYN G. FARQUHAR: In regard to the source of fibrinoid, our pictures can provide no definite answer, but my belief is that fibrinoid is derived from circulating gamma globulins which are for some reason deposited in the subendothelial areas and from there may suffuse through the basement membrane. Hyalin appears to be derived as an extracellular product of the endothelium. There is always a close association between hyalin and endothelium, whereas a clear separation is usually maintained between hyalin and the epithelium.

Finally, in regard to your question about the relationship between proteinuria and the foot process changes, your question indicates there might be discrepancies, but actually there are none. The patient shown with eclampsia and normal foot processes did *not* have significant proteinuria at the time of the biopsy. Another patient with eclampsia *did* show proteinuria and the foot process organization was distorted. Further, we have noted that the foot process changes are not as uniformly severe in those patients with mixed nephrosis-nephritis or the nephrotic syndrome in chronic glomerulonephritis as they are in patients with "pure" nephrosis. Accordingly, as you have mentioned, the degree of proteinuria is usually not so great in patients with the nephrotic syndrome in chronic glomerulonephritis as in patients with "pure" nephrosis.

ALEX B. NOVIKOFF: In your nephrotic syndrome patients, have you encountered glomeruli with relatively large gaps in the basement membrane, as described recently by Spiro[15]?

MARILYN G. FARQUHAR: It should first of all be pointed out that the gaps which Dr. Spiro describes have been seen under rather specific conditions—that is, after staining with phosphotungstic acid. In addition, his illustrations of portions of glomeruli from patients with lipoid nephrosis appear to be advanced lesions with "membranous change". Our studies on pathologic tissues have been from patients with widely varying degrees of glomerular damage and we have not encountered the large gaps in the basement membrane which Dr. Spiro describes. In fact, we have not seen any uniform type of basement membrane lesion

to which we can attribute the disease process. We have described[2,4] a "moth-eaten" appearance of the basement membrane in some patients with nephrosis, but this is not a universal finding. There is a great need at present for definitive experimental evidence to establish not only the mechanism of increased glomerular permeability in nephrosis, but also, as a prerequisite, to establish normal filtration mechanisms. Studies designed to illuminate these problems are now in progress[29, 30].

REFERENCES

1. Mueller, C. B. The structure of the renal glomerulus (review), *Amer. Heart J. 55:* 304-22, 1958.
2. Farquhar, M. G., Vernier, R. L. and Good, R. A. Studies on familial nephrosis, *Amer. J. Path. 33:*791-817, 1957.
3. Farquhar, M. G., Vernier, R. L. and Good, R. A. Application of electron microscopy in pathology: study of renal biopsy tissues, *Schweiz. med. Wschr. 87:*501-10, 1957.
4. Farquhar, M. G., Vernier, R. L. and Good, R. A. An electron microscope study of the glomerulus in nephrosis, glomerulonephritis, and lupus erythematosus, *J. exp. Med. 106:* 649-60, 1957.
5. Vernier, R. L., Farquhar, M. G., Brunson, J. G. and Good, R. A. Chronic renal disease in children, *Amer. J. Dis. Child. 96:*306-43, 1958.
6. Farquhar, M. G., Hopper, J., Jr. and Moon, H. D. Diabetic glomerulosclerosis: electron and light microscopic studies, *Amer. J. Path. 35:*721-55, 1959.
7. Farquhar, M. G. Review of normal and pathologic glomerular ultrastructure. *Proc. 10th ann. Conf. nephr. Syndr.*, Nat. Kidn. Dis. Fdn., Nov. 6-8, 1959, pp. 2-25.
8. Farquhar, M. G. Preparation of ultrathin tissue sections for electron microscopy. A review and compilation of procedures, *Lab. Invest. 5:*317-37, 1956.
9. Jennings, B. M., Farquhar, M. G. and Moon, H. D. Staining methods for osmium-methacrylate sections, *Amer. J. Path.* In press.
10. Bloom, P. M., Hartmann, J. F. and Vernier, R. L. An electron microscopic evaluation of the width of normal glomerular basement membrane in man at various ages, *Anat. Rec. 133:*251, 1959.
11. Piel, C. and Williams, G. F. Long-continued adrenal hormone therapy in childhood nephrosis, *J. Amer. med. Wom. Assoc. 12:*273-279, 1957.
12. Brun, C. and Raaschou, F. Kidney biopsies, *Amer. J. Med. 24:*676-91, 1958.
13. Folli, G. and others. Electronmicroscopic studies of reversible glomerular lesions in the adult nephrotic syndrome, *Ann. intern. Med. 49:*775-95, 1958.
14. Meriel, P. and others. Application de la microscopie électronique à l'étude du rein pathologique: la néphrose lipoidique, *Semaine Hôp. Paris 34:*1674-80, 1958.
15. Spiro, D. The structural basis of proteinuria in man. Electron microscopic studies of renal biopsy specimens from patients with lipid nephrosis, amyloidosis, and subacute and chronic glomerulonephritis, *Amer. J. Path. 35:*47-73, 1959.
16. Vernier, R. L., Papermaster, B. W. and Good, R. A. Aminonucleoside nephrosis. I. Electron microscopic study of the renal lesion in rats, *J. exp. Med. 109:*115-26, 1959.
17. Feldman, J. D. and Fisher, E. R. Renal lesions of aminonucleoside nephrosis as revealed by electron microscopy, *Lab. Invest. 8:*371-85, 1959.
18. Bell, E. T. *Renal diseases.* Phila., Lea and Febiger, 1950, 2nd ed.
19. Allen, A. C. *The kidney, medical and surgical diseases.* New York, Grune & Stratton, Inc., 1951.
20. Jones, D. B. Nephrotic glomerulonephritis. *Amer. J. Path. 33:*313-29, 1957.
21. Churg, J. and Grishman, E. Subacute glomerulonephritis, *Amer. J. Path. 35:*25-46, 1959.
22. Muehrcke, R. C., Kark, R. M., Pirani, C. L. and Pollak, V. E. Lupus nephritis, *Medicine 36:*1-145, 1957.
23. Bergstrand, A. and Bucht, H. Glomerular lesions of diabetes mellitus and their electronmicroscope appearances, *J. Path. Bact. 77:* 231-42, 1959.
24. Geer, J. C., Strong, J. P., McGill, H. C. and Muslow, I. Electron microscopic observations on the localization of amyloid in the kidney in secondary amyloidosis, *Lab. Invest. 7:*554-65, 1958.
25. Miller, F. and Bohle, A. Vergleichende licht- und elektronen-mikroskopische Untersuchungen an der Basalmembran der Glomerulumcapillaren der Maus bei experimentellem Nierenamyloid, *Klin. Wschr. 35:*1204-10, 1956.
26. Pollak, V. E. and others. Reversible glomerular lesions in toxaemia of pregnancy, *Lancet 2:*59-62, 1956.
27. Pappas, G. D., Ross, M. H. and Thomas, L. Studies on the generalized Shwartzman reaction. VIII. The appearance by electron microscopy of intravascular fibrinoid in the glomerular capillaries during the reaction, *J. exp. Med. 107:*333-40, 1958.
28. Vasquez, J. J. and Dixon, F. J. Immunohistochemical analysis of lesions associated with "fibrinoid change," *Arch. Path. 66:*504-17, 1958.
29. Farquhar, M. G. and Palade, G. E. Behavior of colloidal particles in the glomerulus, *Anat. Rec. 133:*378-79, 1959.
30. Farquhar, M. G. and Palade, G. E. Transport of ferritin in the glomerulus after experimental alteration of permeability. Proc. 17th ann. mtg. Electron Microscope Soc. Amer., *J. appl. Physics.* In press.

Application of Thin Section Technique to the Problems of Glomerulonephritis (Abstract)

EDITH GRISHMAN, JACK CHURG, AND WILLY MAUTNER.

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Autopsy and biopsy specimens of normal glomeruli and diffuse glomerulonephritis were investigated by thin (0.5 micron) sections and electron microscopy. Thin sections were found to be a valuable link between conventional light and electron microscopy.

Blocks were embedded in celloidin paraffin or in methacrylate. Thin sections were stained with PAS, periodic acid silver methenamine, and chromotrope aniline blue with greatly prolonged staining times.

In normal human glomeruli the existence of intercapillary spaces could be demonstrated. Electron microscopic sections showed thin branches of basement membrane separating the intercapillary space from the capillaries and endothelial cells, and a few cells within the intercapillary space. This space plays an important role in pathologic conditions. The inflammatory process in acute glomerulonephritis takes place in the intercapillary space, and is characterized by exudative and proliferative changes which lead eventually to ballooning of lobular centers and compression of capillaries. This process usually regresses. However, if complete resolution does not follow, fibers may appear in the intercapillary space and signal the onset of the subacute stage.

The histopathologic picture of subacute glomerulonephritis, as seen in thin light microscopy sections, is very complex. It comprises intercapillary inflammation and fiber formation, deposition of hyalin, crescent formation, and capillary wall thickening. This capillary wall thickening may be caused by deposition of homogeneous hyalin between the endothelium and the basement membrane resembling closely the "wire loops" of disseminated lupus erythematosus. Another type of capillary wall thickening, frequently associated with the nephrotic syndrome, consists of a broad non-homogeneous zone between the basement membrane and the epithelial cells. The zone is composed of bands perpendicular to the basement membrane spaced 0.5 to 1.0 micron apart. With chromotrope anilin blue stain, hyalin material can be demonstrated between the bands. This type of change is called "membranous transformation." Electron microscopic studies of biopsy specimens in cases of subacute glomerulonephritis permitted the observation of early changes of the capillary wall, resembling membranous transformation. They consisted of variation in density and thickness of basement membranes and deposits of homogeneous material between the foot processes of the epithelial cells. It is suggested that this material may be trapped protein which has leaked through the damaged basement membrane. Changes of foot processes with the formation of sheets of cytoplasm were also observed.

Thickening of the capillary wall may also be caused by splitting and wrinkling of the basement membrane. Somewhat similar splitting of basement membranes was seen electronmicroscopically in rat glomeruli during experimental glomerulonephritis of the Masugi type.

The essential feature of chronic glomerulonephritis is glomerular obsolescence with collapse of capillaries. This obsolescence can be brought about by a variety of changes, such as intercapillary fibrosis and hyalinization or capillary wall alterations. In the latter case a seemingly hyalinized glomerulus consists of nothing but a tangle of basement membranes which may be involved by the disease process, i.e., split, wrinkled, or the seat of membranous transformation. Pure capillary collapse is usually the result of arterio- and arteriolosclerosis.

The recognition of the specific type of glomerular obsolescence is particularly important for the interpretation of renal biopsies in which the majority of glomeruli may be obsolete.

DISCUSSION

MONROE BIRNS: Is it possible to explain some of the "intercapillary spaces", as for example a cross section of a capillary which has turned upon itself, enabling one to have at the same time the appearance of a cross section of two vessels cut tangentially through the basement membrane?

EDITH GRISHMAN: We have seen such tangential sections in thin sections, but they look quite different from the intercapillary spaces we have demonstrated. In tangential sections one may see endothelial cells between two capillaries. However, these cells are never separated from the lumen by thin membranes, while the intercapillary space is distinctly separated.

Xanthogranulomatous Pyelonephritis (Abstract)

GORDON ROSS HENNIGAR

Institute of Pathology, State University of New York Downstate Medical Center, Brooklyn, New York

Fourteen cases of an uncommon type of pyelonephritis with xanthogranulomatous change are described. Six were associated with renal lithiasis, while eight were not associated with inflammatory or obstructive uropathy. All but one were unilateral.

Clinically, the duration of all cases exceeded one year. Hypertension was present in two cases and diabetes in one.

Grossly, the kidneys were of normal size or enlarged and had a distinctive appearance characterized by foci of pale or yellow nodules. In some cases there was resemblance to tuberculosis, while in others similarity to renal tumor was striking.

Histologically, lipid and non-lipid granular histiocytes predominated in the picture. In addition, giant cells were seen here and there and plasma cells were abundant. In advanced lesions fibrous tissue and smooth muscle were seen.

Bacteriologically, organisms of the Proteus group were isolated in pure or mixed culture from 10 of the 14 cases. This group of organisms is frequently found in chronic renal infections. Whether the incidence of xanthogranulomatous pyelonephritis is increased since the advent of chemotherapy requires clarification.

BIBLIOGRAPHY

1. Barrie, H. J. Foam cell granuloma in chronic pyonephrosis simulating tuberculosis, *Brit. J. Surg. 36*:316-19, 1948.
2. Ghosh, H. Chronic pyelonephritis with xanthogranulomatous change, *Amer. J. clin. Path. 25*:1043-49, 1955.
3. Larson, W. P. and Bell, E. T. A study of the lesions produced by *Bacillus proteus*, *J. infect. Dis. 13*:510-11, 1913.
4. Mack, F. G. and Mador, M. L. Pyogenic (foam cell) granuloma in a case of pyonephrosis, *J. Urol. 67*:258-61, 1952.
5. Putscher, W. Die entzündlichen Erkrankungen der ableitenden Harnwege und deren Nierenhüllen einschliesslich der Pyelonephritis und der Pyeonephrose. In *Handb. spez. Path. Anat. Histol.*, O. Lubarsch and F. Henke, edits. Berlin, J. Springer, 1934, v. 6, ed. 2 p. 453.

DISCUSSION

MORRIS F. WIENER: Were there any instances of congenital renal malformation in your series of cases of xanthogranulomatous pyelonephritis? I have a case which involved the right kidney that had the shape of a horse-shoe.

Possible etiologies of this uncommon and striking lesional process are suggested in a 1955 report of three cases of chronic pyelonephritis with xanthogranulomatous change (see reference 2 above). Mention is made of various antibiotics and sulfa drugs which sterilize the usual pathogens and leave the resistant *B. proteus* as the causative agent. The drugs and antibiotics themselves may be an important factor by changing the pathogenetic character of the bacteria, or by altering the tissue reaction in some obscure way.

GORDON R. HENNIGAR. In reply to Dr. Wiener's question, we were not fortunate enough to have any instances of congenital renal malformation in our cases of xanthogranulomatous pyelonephritis.

THE NEW YORK ACADEMY OF MEDICINE

FOURTH ANNUAL POSTGRADUATE WEEK

OCTOBER 24 to 28, 1960

FRONTIERS IN MEDICINE AND SURGERY — 1960

PANEL MEETING — 4:30 P.M.

Monday October 24

RECOGNITION AND MANAGEMENT OF COMMON VIRAL DISEASES

Moderator: YALE KNEELAND, JR., M.D., *College of Physicians and Surgeons, Columbia University*

LECTURES — 8 P.M.

GENETICS

G. W. BEADLE, Ph.D., *California Institute of Technology*

GENETICAL VARIATIONS IN THE SERUM PROTEINS OF MAN

ALEXANDER G. BEARN, M.D., *The Rockefeller Institute*

PANEL MEETING — 4:30 P.M.

Tuesday October 25

ARTERIAL OBSTRUCTION IN THE EXTREMITIES: MEDICAL AND SURGICAL ASPECTS

Moderator: JERE W. LORD, JR., M.D., *New York University Post-Graduate Medical School*

LECTURES — 8 P.M.

CLINICAL IMPLICATIONS OF CYANOSIS

HARRY W. FRITTS, JR., M.D., *New York University College of Medicine*

PRESENT UNDERSTANDING OF THE ROLE OF GLIADIN IN THE STEATORRHEA SYNDROMES

CHARLES D. MAY, M.D., *College of Physicians and Surgeons, Columbia University*

PANEL MEETING — 4:30 P.M.

Wednesday October 26

"AUTO-ANTIBODIES" AND DISEASE

Moderator: HENRY G. KUNKEL, M.D., *The Rockefeller Institute*

LECTURES — 8 P.M.

CURRENT STATUS OF BONE MARROW TRANSPLANTATION

J. W. FERREBEE, M.D., *College of Physicians and Surgeons, Columbia University*

LECTURES — 8 P.M. (continued)

Wednesday October 26 *(continued)*

CURRENT STATUS OF BONE TRANSPLANTATION
CAPTAIN G. W. HYATT, MC, USN, *U. S. Naval Medical College*

CURRENT STATUS OF KIDNEY TRANSPLANTATION
JOSEPH E. MURRAY, M.D., *Harvard Medical School*

PANEL MEETING — 4:30 P.M.

Thursday October 27

THE VALUE OF ANTIBACTERIAL PROPHYLAXIS IN MEDICAL AND SURGICAL PROCEDURES
Moderator: WALSH McDERMOTT, M.D., *Cornell University Medical College*

LECTURES — 8 P.M.

MUSCULAR DISEASE
DAVID GROB, M.D., *State University of New York, Downstate Medical Center*

PYELONEPHRITIS
EDWARD A. GALL, M.D., *University of Cincinnati College of Medicine*

PANEL MEETING — 4:30 P.M.

Friday October 28

RECOGNITION AND MANAGEMENT OF THE COMMON PSYCHONEUROSES
Moderator: DANA W. ATCHLEY, M.D., *College of Physicians and Surgeons, Columbia University*

LECTURES — 8 P.M.

NUTRITION AND THE BRAIN
RAYMOND D. ADAMS, M.D., *Harvard Medical School*

SURGICAL ASPECTS OF INTERNAL CAROTID OBSTRUCTION
MICHAEL E. DeBAKEY, M.D., *Baylor University College of Medicine*

NEUROLOGICAL ASPECTS OF INTERNAL CAROTID OBSTRUCTION
H. HOUSTON MERRITT, M.D., *College of Physicians and Surgeons, Columbia University*

BUFFET SUPPER

A limited number of guests can be accommodated each evening for buffet supper, at $3.75 per person, in the Presidents' Gallery from 5:30 to 7:30 p.m. ADVANCE REGISTRATION AND CHECK (payable to The New York Academy of Medicine) must be received no later than MONDAY, OCTOBER 17, 1960.

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Squibb Alpha-Phenoxyethyl Penicillin Potassium

new chemically improved penicillin which provides the highest blood levels that are obtainable with oral penicillin therapy

As a pioneer and leader in penicillin therapy for more than a decade, Squibb is pleased to make Chemipen, a new chemically improved oral penicillin, available for clinical use.

With Chemipen it becomes possible as well as convenient for the physician to achieve and maintain higher blood levels—with greater speed—than those produced with comparable therapeutic doses of potassium penicillin V. In fact, Chemipen is shown to have a 2:1 superiority in producing peak blood levels over potassium penicillin V.*

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And the economy for your patients will be of particular interest—Chemipen costs no more than comparable penicillin V preparations.

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Supply: Chemipen Tablets of 125 mg. (200,000 u.) and 250 mg. (400,000 u.), bottles of 24 tablets. Chemipen Syrup (cherry-mint flavored, nonalcoholic), 125 mg. per 5 cc., 60 cc. bottles.

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*Knudsen, E. T., and Rolinson, G. N.: Lancet 2:1105 (Dec. 19) 1959.

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The first specific aldosterone-blocking agent...

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effectively extends the medical control of edema or ascites.
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satisfactory relief of resistant or advanced edema even when all other agents, alone or in combination, are ineffective or are only partially effective.

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ALDACTONE acts by blocking the effect of aldosterone, the principal mineralocorticoid governing the reabsorption of sodium and water in the distal segment of the renal tubules.

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It is fully expected that Aldactone will change present medical concepts of the therapeutic limitations of managing edema. Many patients living in a greater or lesser state of edematous invalidism can now be edema-free. To others, gravely ill, Aldactone will be life-saving.

When used alone, Aldactone will produce a satisfactory diuresis in about half of those patients whose edema is resistant to conventional diuretic agents.

When Aldactone is used in a comprehensive therapeutic regimen, which includes a mercurial or a thiazide diuretic, a satisfactory diuresis and relief of edema may be expected in approximately 85 per cent of edematous patients *who would not otherwise respond.*

DOSAGE: For most adult patients the optimal dosage of Aldactone, brand of spironolactone, is 100 mg. four times daily. Aldactone should be administered for at least four or five days before appraising the initial response, since the onset of therapeutic effect is gradual when it is used alone. Aldactone manifests accelerated activity with greater response as early as the first and second days when used in combination with a mercurial or thiazide diuretic.

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"It is now well recognized that serum cholesterol levels in man can be lowered by the judicious substitution of one type of dietary fat for another. However, it is relevant to inquire whether a patient can be assured that such a radical change in his dietary habits will prevent coronary occlusion or a cerebral vascular accident. This question must unfortunately be answered in the negative, for it has not been proved that lowering the level of serum cholesterol will prevent either the occurrence or the end-results of atherosclerosis. At the present time, clear proof of this proposition still seems many years away. Nevertheless, there are many reasons for believing that there is some connection between cholesterol metabolism and atherosclerosis, and, while waiting for elucidation of this relationship by laboratory workers, it seems justifiable to apply certain dietary procedures that are theoretically harmless and possibly beneficial."

Excerpted from J.A.M.A., Aug. 29, 1959

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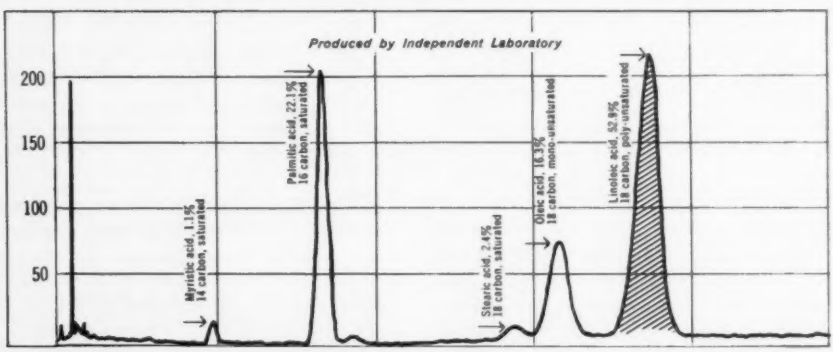

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Wesson is 100% cottonseed oil . . . winterized and of selected quality

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Total unsaturated	70-75%
Palmitic, stearic and myristic glycerides (saturated)	25-30%
Phytosterol (predominantly beta sitosterol)	0.3-0.5%
Total tocopherols	0.09-0.12%

Never hydrogenated—completely salt free

Each pint of Wesson contains 437-524 Int. Units of Vitamin E

Where a vegetable (salad) oil is medically recommended for a cholesterol depressant regimen, Wesson is unsurpassed by any readily available brand.

To be effective, a diet must be *eaten* by the patient. The majority of housewives prefer Wesson,* particularly by criteria of odor, flavor (blandness) and lightness of color.

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*Reconfirmed by recent tests against the next leading brand with brand identifications removed, among a national probability group.

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Dosage: One tablet one-half to one hour before each meal.

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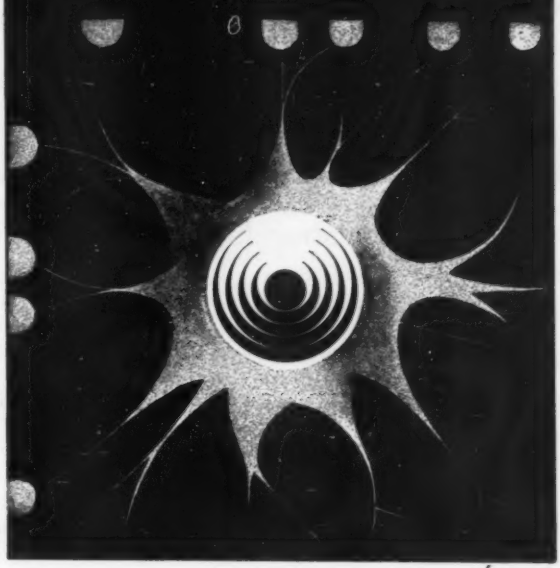
brand of imipramine HCl

in depression

lights the road to recovery
in 80 per cent of cases



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Tofrānil
a potent thymoleptic . . . not a MAO inhibitor.

Does act effectively in *all* types of depression regardless of severity or chronicity.

Does not inhibit monoamine oxidase in brain or liver; produce CNS stimulation; or potentiate other drugs such as barbiturates and alcohol.

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References: 1. Ayd, F. J., Jr.: Bull. School Med., Univ. Maryland *44*:29, 1959. 2. Azima, H., and Vispo, R. H.: A.M.A. Arch. Neurol. & Psychiat. *81*:658, 1959. 3. Lehmann, H. E.; Cahn, C. H., and de Verteuil, R. L.: Canad. Psychiat. A. J. *3*:155, 1958. 4. Mann, A. M., and MacPherson, A. S.: Canad. Psychiat. A. J. *4*:38, 1959. 5. Sloane, R. B.; Habib, A., and Batt, U. E.: Canad. M.A.J. *80*:540, 1959. 6. Straker, M.: Canad. M.A.J. *80*:546, 1959. 7. Strauss, H.: New York J. Med. *59*:2906, 1959.

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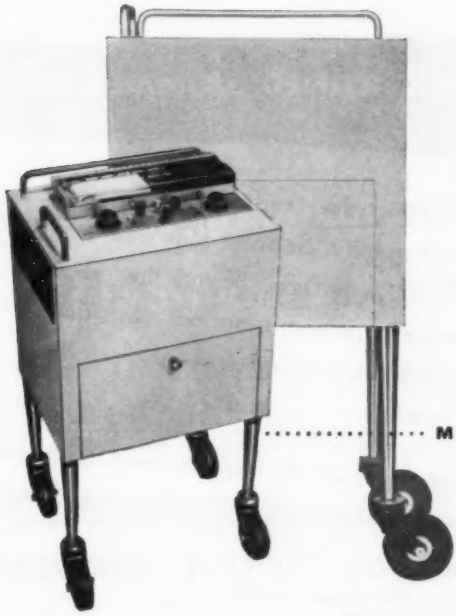

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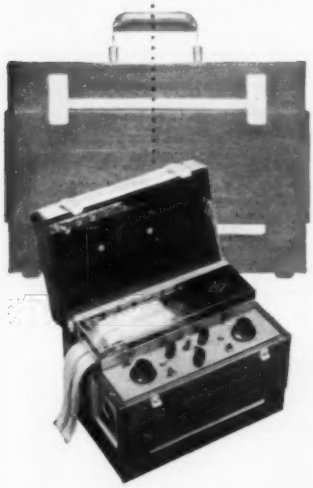

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meprobamate **plus** d-amphetamine...suppresses appetite...elevates mood... reduces tension...**without** insomnia, overstimulation or barbiturate hangover.

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ALTAFUR was found "highly satisfactory in most of the primary and secondary bacterial dermatoses treated to date," including "pyodermas . . . caused by antibiotic resistant strains of staphylococci."[1] In a nationwide survey[2] there were **94%** satisfactory results (cured or improved) among 159 patients treated with ALTAFUR for pyodermas.

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99.5% of isolates (214 of 215) from patients with staphylococcal infections—including many antibiotic-resistant strains—proved sensitive in vitro to ALTAFUR in tests conducted across the nation.[3] **99.7%** of staphylococcal isolates (334 of 335) at a large general hospital—including many antibiotic-resistant strains—proved sensitive in vitro to ALTAFUR.[4]

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"Because of its relationship to previously developed nitrofurans, it is anticipated that [ALTAFUR] will retain its original spectrum after longstanding clinical usage."[5] Development of significant bacterial resistance to ALTAFUR has not been encountered to date.[6]

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Side effects are easily avoided or minimized by these simple precautions: 1) *alcohol should not be ingested in any form, medicinal or beverage, during* ALTAFUR *therapy and for one week thereafter* 2) each dose should be taken with or just after meals, and with food or milk at bedtime (to reduce the likelihood of occasional nausea and emesis).

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1. Weiner, A. L.: Paper presented at the Conference on Recent Advances in the Treatment of Chronic Dermatoses, University of Cincinnati (Ohio), Nov. 5, 1959. 2. Compiled by the Medical Department, Eaton Laboratories, from case histories received. 3. Christenson, P. J., and Tracy, C. H.: Current Therapeutic Research 2:22, 1960. 4. Glas, W. W., and Britt, E. M.: Proceedings of the Detroit Symposium on Antibacterial Therapy, Michigan and Wayne County Academies of General Practice, Detroit, Sept. 12, 1959, p. 14. 5. Leming, B. H., Jr.: Ibid., p. 22. 6. Investigators' reports to the Medical Department, Eaton Laboratories.

Tablets of 250 mg. (adult)

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Because a swift-acting spermicide best meets the variables of spermatozoan activity.

Lanesta Gel, "...found to immobilize human spermatozoa in one-third to one-eighth the time required by five of the leading contraceptive products currently available . . ."* thus provides the *extra* margin of assurance in conception control. The accelerated action of Lanesta Gel — it kills sperm in minutes instead of hours — may well mean the difference between success and failure.

**Berberian, D. A., and Slighter, R. G.: J.A.M.A.* 168:2257 *(Dec. 27) 1958.*

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Supplied: Lanesta Exquiset . . . with diaphragm of prescribed size and type; universal introducer; Lanesta Gel, 3 oz. tube, with easy clean applicator, in an attractive purse. Lanesta Gel, 3 oz. tube with applicator; 3 oz. refill tube — available at all pharmacies.

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reactivates the geriatric patient

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reactivates the convalescent

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Each tablet, 100 mg. METRAZOL. Each teaspoonful, 100 mg. METRAZOL and 1 mg. thiamine.

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Each teaspoonful, 100 mg. METRAZOL, 10 mg. niacinamide, 1 mg. each of thiamine, riboflavin, pyridoxine, and 2 mg. d-panthenol. Each tablet, in addition, 25 mg. vitamin C.

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meprobamate **plus** d-amphetamine... depresses appetite...elevates mood... eases tensions of dieting...**without** over-stimulation, insomnia or barbiturate hangover.

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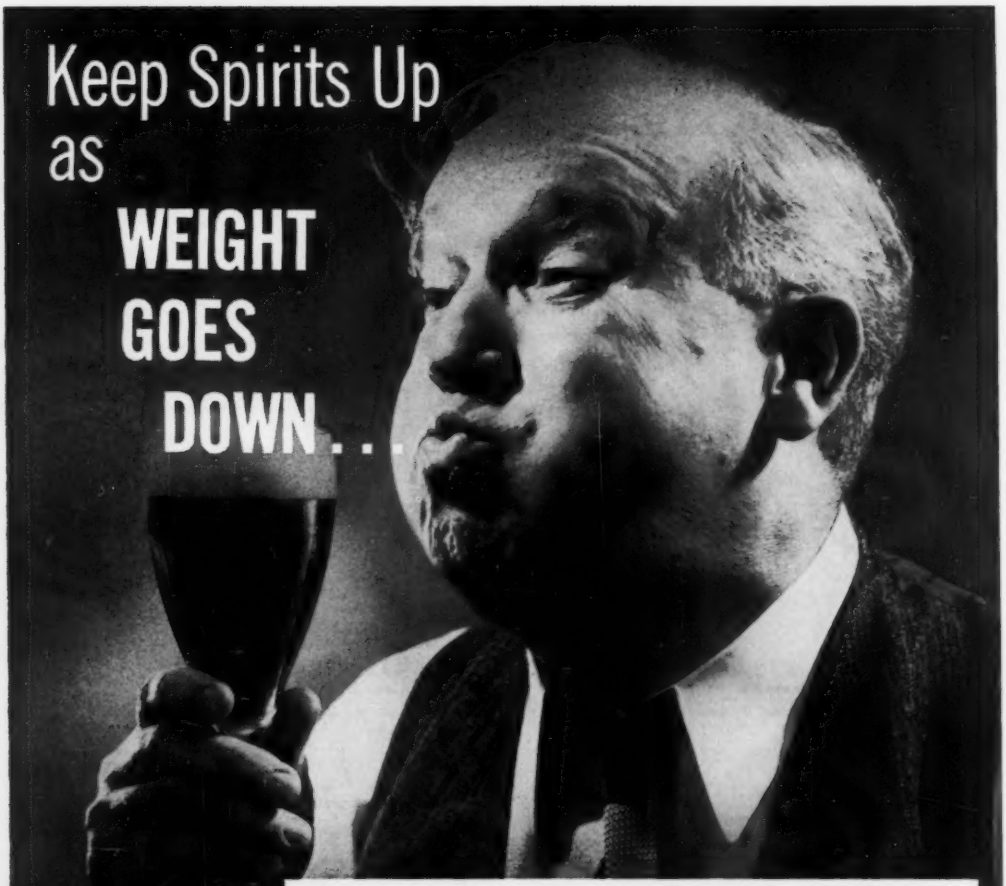

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Ref: Plotz, M.: Modern Management of Obesity, J.A.M.A. 170: 1513-1515 (July 25) 1959.

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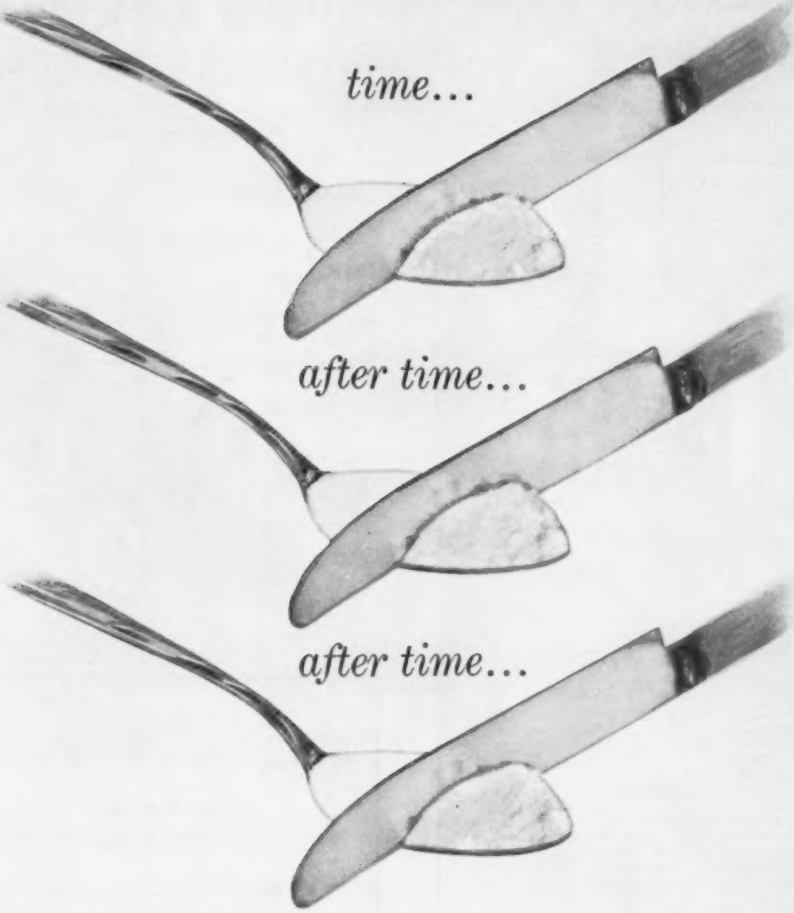

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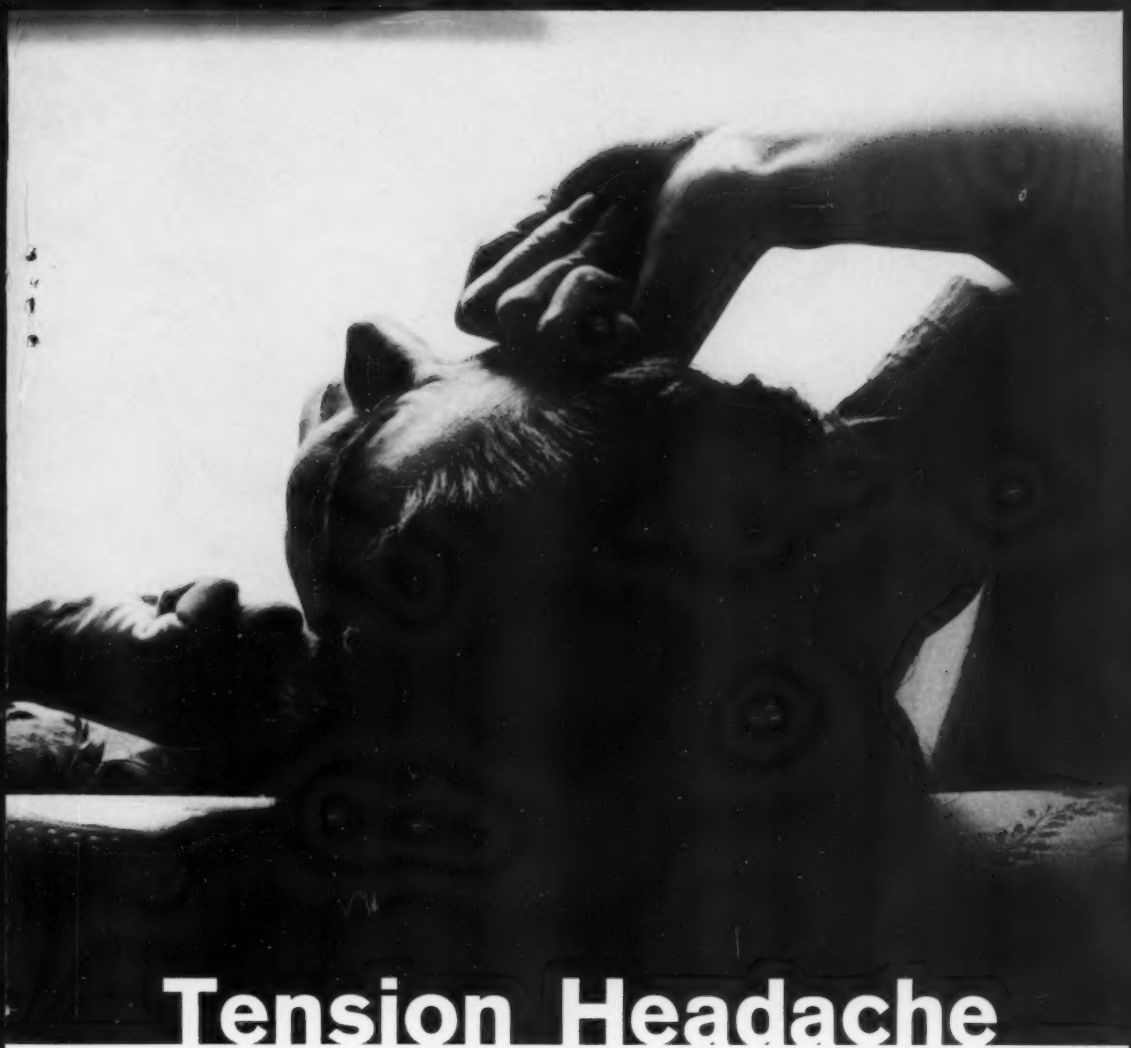

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Blumenthal, L.S., and Fuchs, M.: Am. Pract. & Digest Treat. 9:1121 (July) 1958.

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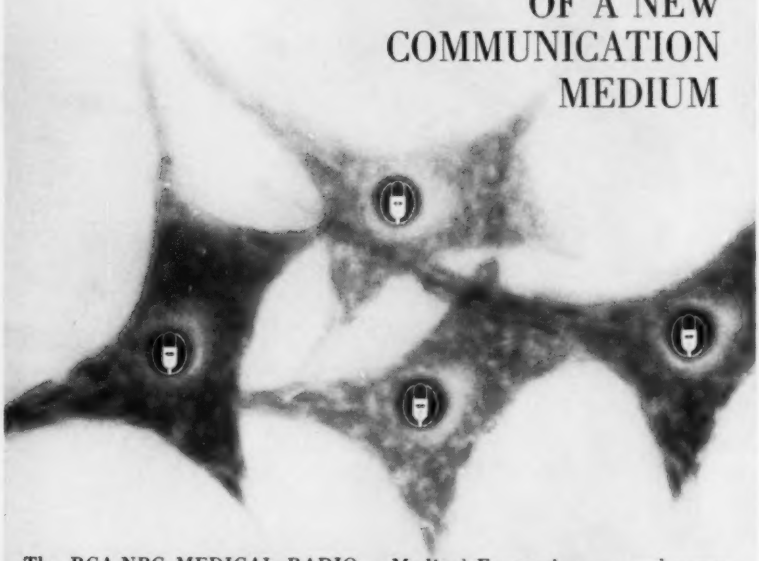

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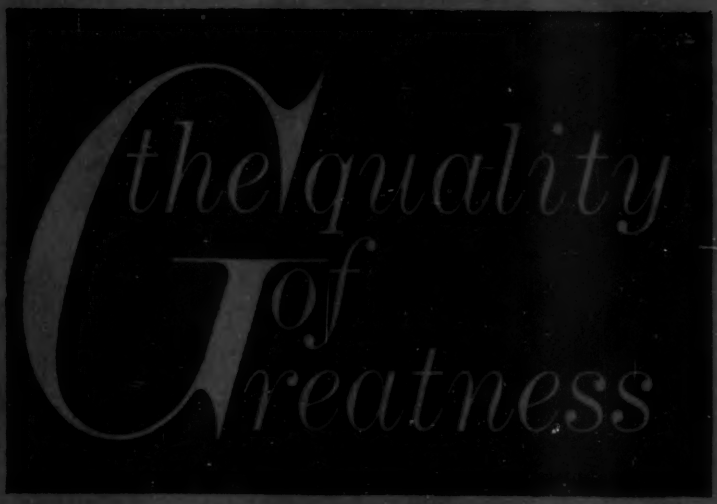

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